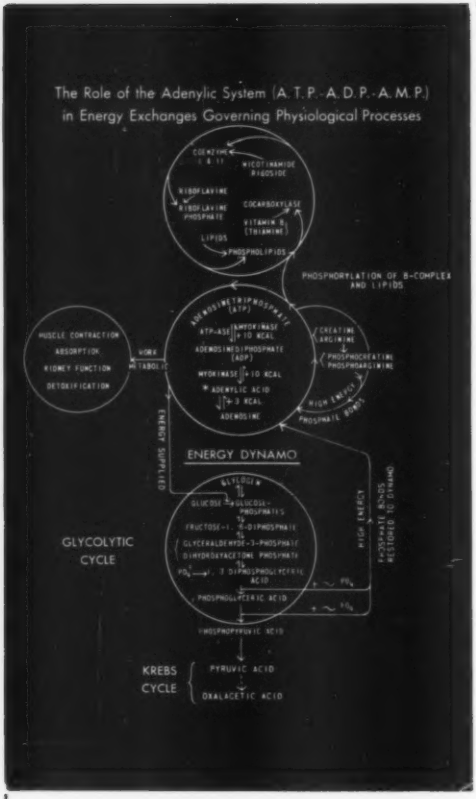
Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

APRIL--1956
Volume 6 — Number 4



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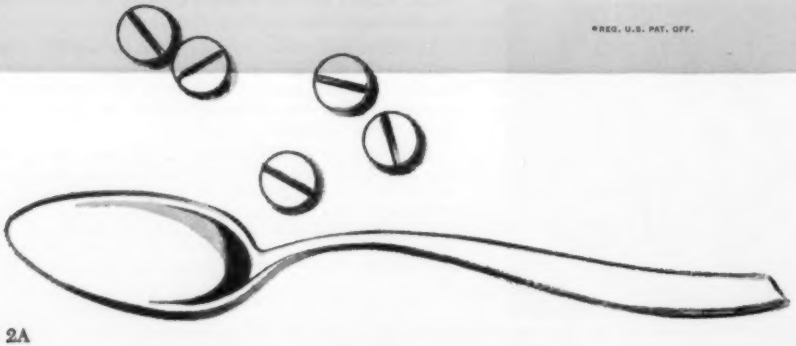

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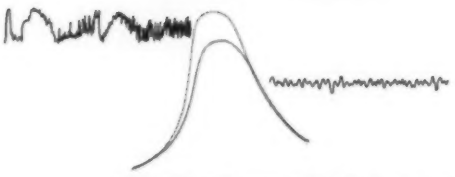

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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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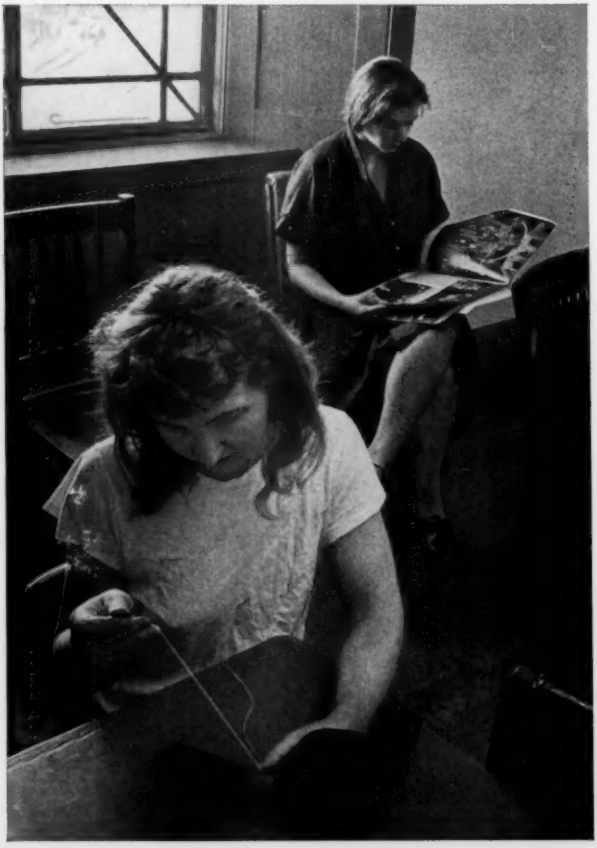

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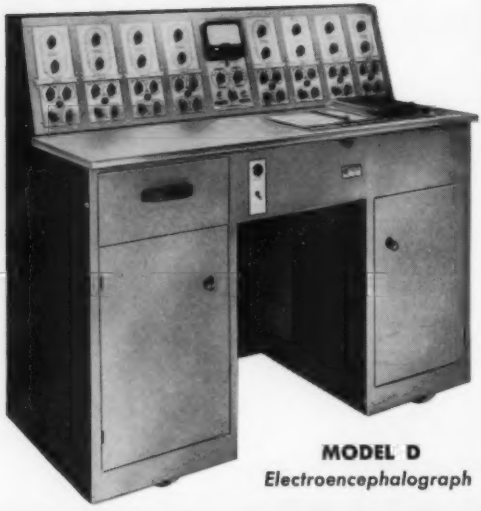

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Volume 6 Neurology Number 4

Hereditary Light Sensitive Epilepsy

Sherwood Davidson, M.D. and C. Wesley Watson, M.D.

THE OCCURRENCE OF SEIZURES as the result of an externally applied stimulus is an ancient observation. The rotation of a potters wheel before the eyes of a slave offered for sale in the Greek market place was used as a test of his susceptibility to epilepsy, the whirling wheel having been found on occasion to provoke a seizure.[1]

Light has been observed to be an adequate stimulus among others for the precipitation of seizures or myoclonus and cerebral electrical abnormalities.[2–20] Such a sensitivity is often suggested by the patient's own history of the precipitation of seizures by light.[5,7,14,21,22] Light sensitivity in terms of evoked cerebral electrical abnormalities with or without the precipitation of myoclonus and clinical seizure phenomena has been found to occur in a significant proportion of patients with idiopathic epilepsy[13,16] but not in a significant proportion of entirely "normal" control subjects.[16,23,24]

Recent observations in a series of families in which light sensitivity and seizure phenomena occur suggested the importance of light sensitivity as evidence of genetically determined cerebral dysfunction. We have now observed 16 such families, including two with identical twins.

Light sensitivity as a symptom of diffuse neuronal disease has been observed to occur in individuals suffering the progressive syndrome of myoclonus epilepsy.[3,4,9,18]

The occurrence of cryptogenic seizures in one generation and partial or arrested forms of the syndrome of myo-

From the department of neurology, neurosurgery, and psychiatry, New England Center Hospital, and the department of medicine, Tufts University Medical School, Boston, Massachusetts.

With the technical assistance of Reinette Bowker and Muriel Preston.

Read at the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 29, 1955.

This study was aided by funds provided through Grant B-566 by the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, Department of Health Education and Welfare.

clonus epilepsy with its implication of diffuse nerve cell affection in another generation has been pointed out by Watson and Denny-Brown.[18]

Lennox[25] in an excellent study of 200 twin pairs has shown that among monozygotic twins without brain damage the concordance of epilepsy both absolute and compared with other twins is quite high (70.1 per cent) and that this concordance extends to electroencephalographic abnormalities. Lennox has shown further[26] that the incidence of seizures among the relatives of individuals with seizures is slightly but significantly higher than among the general population. The proportion of individuals in the total epileptic population who have seizures as a result of some genetically determined predisposing susceptibility has been much more difficult to ascertain.

That genetically determined predisposition is not essential for the development of seizures which follow trauma was the inference to be drawn from the observation that over 40 per cent of persons with penetrating gunshot wounds producing brain damage developed seizures, although the incidence of seizures among their relatives was not increased over that of the general population.[27] Therefore, it becomes pertinent to inquire whether, within the group designated clinically as "idiopathic" or "cryptogenic" epilepsy, there exist individuals in whom there is indeed a genetically determined susceptibility to seizures. While there is general agreement that heredity plays some role in epilepsy, the difficulty heretofore has been that when those suffering seizures are analyzed statistically as a group, the designation of susceptible individuals has been possible only in relation to the development of seizures in other members of the same family or by the relatively infrequent finding of a distinctive electroencephalographic abnormality.[28]

The occurrence of light sensitivity in identical twins has been reported,[12] and the occurrence of "photogenic epilepsy" in a family setting affecting individuals in more than one generation has also been cited.[14] Fairweather, O'Sullivan, and Walter[9] described "photogenic epilepsy" in identical twins with Univerricht's myoclonus epilepsy. Walter and Walter[10] remarked upon "pathologic effects" in the electroencephalograms of individuals with no personal record of seizures but with seizures occurring in others in the family.

In the multitude of reports that have accumulated on these subjects, the clinical significance of light sensitivity as one manifestation of a genetically determined central nervous system disease has not previously been emphasized.

MATERIAL AND METHOD

Electroencephalographic recordings during intermittent retinal illumination and hyperventilation were performed on 615 persons, including four sets of identical twins.* Fifty-two individuals of 16 families were studied further because of stimulus sensitivity occurring in 39 of them. Cerebral electrical activity was recorded by means of an eight channel Grass electroencephalograph. Eight or 16 electrodes spaced equidistant applied with Bentonite paste were used, with scalp-to-scalp or scalp-to-ear linkages during recording. Intermittent high intensity short duration retinal illumination was carried out with the Grass model PS-1 photic stimulator at variable frequencies, intensity, and with single

*These twins are part of a series of 200 pairs studied by Dr. William G. Lennox.[26] They were examined at his suggestion and with his kind permission.

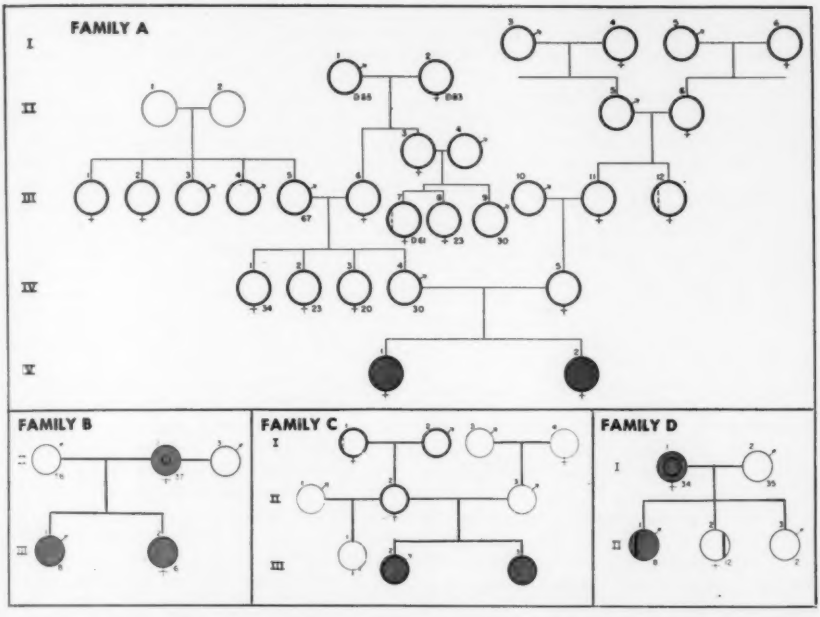

FIG. 1. Pedigrees of families A, B, C, and D. The following convention applies also to figures 7, 8, and 9. Cases are designated in the text by generation (Roman numeral) and case number (Arabic numeral). The families are designated alphabetically by upper case letters. Vertical stripes indicate light sensitivity. Double concentric circles indicate that the person has had seizures. A small inner circle indicates that seizure phenomena or aura were precipitated by light stimulus. Horizontal stripes indicate precipitation by light of sleep rhythms in an individual with narcolepsy (case III 4 Family O). A vertical single stripe indicates adult enuresis (case II 1 Family F) or a "behavior problem" (case II 1 Family D). A single vertical interrupted stripe indicates acquired neurologic disease. The horizontal bar (Families G and J) indicates episodic hemicephalalgia. The solid center "bull's eye" indicates the precipitation of a generalized seizure by intermittent retinal illumination in the asymptomatc father of identical epileptic twins. The vertical bar on the right side indicates electroencephalographic abnormality on hyperventilation (case II 2 Family D). Vertical bar in center (case IV 2 Family G) indicates reported electroencephalographic abnormality in resting record. Interrupted inner circle (case II 3 Family E) indicates death in infancy after frequent febrile seizures. Cases examined to June 1955 are designated in the protocols.

and paired flashes. Recording was performed with patients supine and the eyes open and closed. The patterned source was diffused as required by the interposition of translucent diffusion material between it and the patient's eyes. Tests were performed in a room with a dim overhead light or, as required, in absolute darkness. No Metrazol or other pharmacologic agents were employed.

CASE HISTORIES AND FINDINGS

FAMILY A (figure 1)

Case V 1. C. S., a seven year old girl, was seen in the neurological out-patient department because of the complaint of "spasms of turning up of the head and eyes for about one year." She was born of a normal full-term delivery, developed well, and had previous seizures only during an episode of "meningitis" in 1952. The patient's parents and grandparents were asymptomatic. A female sibling aged four years (K. S., case V 2) had no history of seiz-

ures. A maternal great aunt (R. L., case III 12) has been in a state hospital for epileptics for 20 years because of seizures and mental deficiency since birth. Examination of this aunt in November 1954 revealed asymmetric spastic quadriparesis with no definite evidence of progression since birth. A paternal second cousin (case III 7) has had generalized seizures.

During the patient's hospitalization in 1952 she had fever, headache, and anorexia for three days, with vomiting and several generalized seizures on the day of admission. She was stuporous for the first 24 hours, with a temperature elevation to 106° F. and four generalized seizures. The diagnosis of meningitis due to *H. influenza* was established by identification of the organism. At the time of her discharge she displayed altered and disturbed behavior. Mental status examination revealed no abnormalities; performance was "superior."

In 1954 there were frequent episodes of sudden transient upward gaze, with fluttering of eyelids and extension of head. The patient had found that these could be prevented by willed inhibition of blinking or by staring fixedly and unblinking at an object. The patient has been doing somewhat poorer than usual in her school work.

Neurologic examination revealed a normal mental status. The patient displayed recurrent episodes of sudden bilateral simultaneous symmetric elevation of eyebrows, upper eyelids, and upward deviation of both eyes associated with a simultaneous extension of the head and sudden dropping of the mandible. The movements were repeated three or four times beginning rhythmically but interrupted by spasm.

Laboratory studies showed that complete blood count, urinalysis, and blood Hinton were normal. Roentgenograms of skull were normal.

Electroencephalographic findings. C. S., *Case* V 1 (figure 2): With eyelids closed in room-light and during intermittent retinal illumination as well as during the interposition of a translucent diffusion material between the patterned light source and the patient's eyes, a bilateral, symmetric, generally synchronous discharge of excessive relative amplitude was seen which took the form of multiple spikes and slow waves of variable frequency within the range of 2 to 5 cycles per second. The initial response was likely to be that of multiple spikes exhibiting progressive augmentation of amplitude during a burst occurring over a 1/10 or 2/10 second epoch, followed by a series of slow waves in the 1 to 3 cycles per second frequency range, following which there occurred very slow activity in the ¼ to ½ cycle per second range. The abnormal response was of greatest prominence in those leads corresponding to the occipitoparietal region. The initial polyphasic spike discharge was confined to the occipitoparietal region, while the slow activity which followed appeared throughout the entire recording area bilaterally, simultaneously, and synchronously. Precipitation of the evoked cerebral electrical abnormality did not occur with eyelid opening or eyelid closure in total darkness. At just supraliminal frequency and intensity the occlusion of one eye with the resultant diminution by one-half of retinal area illuminated was sufficient to prevent the appearance of the evoked cerebral electrical abnormality. Without altering the conditions of stimulation with uncovering of both eyes with resultant exposure of both retina to the flashing light, the cerebral electrical abnormality again was consistently evoked. At just subliminal parameters of frequency and intensity the cerebral electrical abnormality described could be consistently evoked by the interposition of a translucent diffusing material (white bond typewriter paper). This occurred despite the concomitant demonstrable reduction in intensity of the illumination. The discharge took the form of a slightly or grossly arrhythmical spike and dominant rhythm in the occipital and parietal region in the ca. 8 to 9 per second frequency range. In the frontal region there was a very high amplitude, discrete wave form, regular ca. 30 per second discharge which was bilateral and symmetric. In the resting trace throughout the entire recording area there was scattered slow activity in the 4 to 7 per second frequency range, scattered spike discharges occurring singly or in multiples which are generally bilateral, symmetric, and synchronous. There was in addition a ca. 4 per second rhythmically repeated slow wave discharge alternating with faster frequencies and showing first gradual augmentation of amplitude and then gradual decrease in amplitude of successive slow waves. Throughout the entire resting trace with eye closure in dimly lighted room a precipitation of the cerebral electrical abnormality occurred consistently with retinal illumination or with

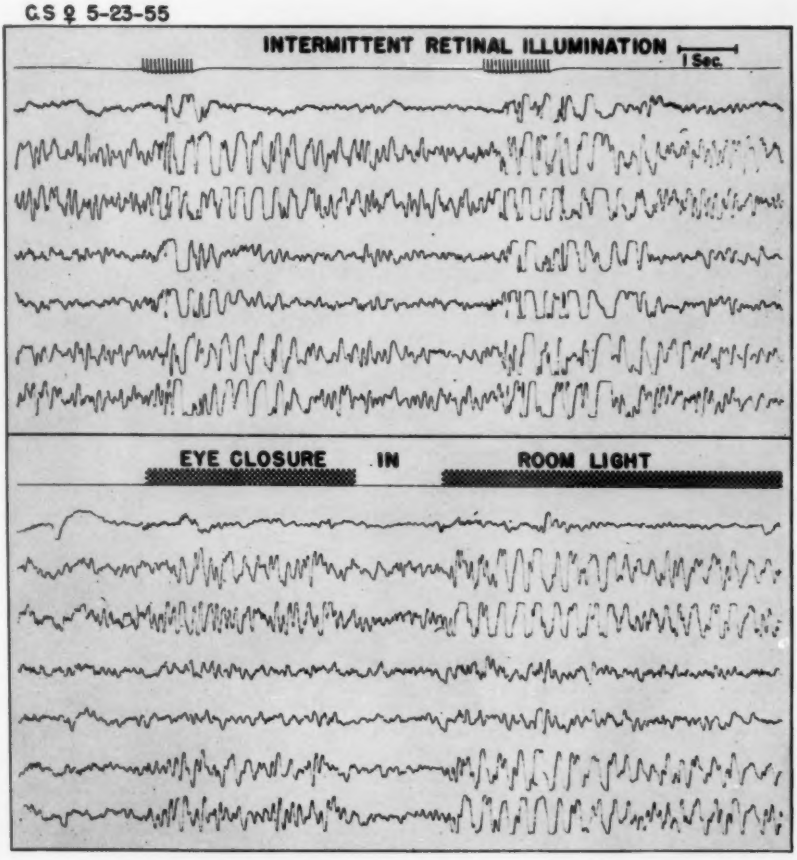

FIG. 2. Cerebral electrical activity of C. S. (case V 1 Family A) during bilateral intermittent retinal illumination (upper panel) and during eyelid opening and closure (lower panel) in room light. Period of eyelid closure is indicated by cross hatched bar. Channel 1. Photoelectric cell. 2. Right orbicularis oculi muscle. 3. Left parietal-occipital. 4. Right parietal-occipital. 5. Left frontal-temporal. 6. Right frontal-temporal. 7. Left temporal-occipital. 8. Right temporal-occipital.

diffusion of this light over the retina by interposed translucent substance. While the evoked and "spontaneous" discharges described are generally bilaterally symmetric and synchronous, it is notable that there are frequent minor differences in amplitude of the discharges when one side is compared with the other. Occasionally the abnormal discharge would occur predominantly on one side almost to the exclusion of the other. There was no consistent lateralization or localization of the discharges, however, even though inconstant minor asymmetric prominences of amplitude were the rule.

Electroencephalographic findings. K. S., *Case* V 2, 11-10-54 (figure 3): Examination of the resting trace revealed the same features as those described for that of the patient's sister (case V 1) except that during the resting trac-

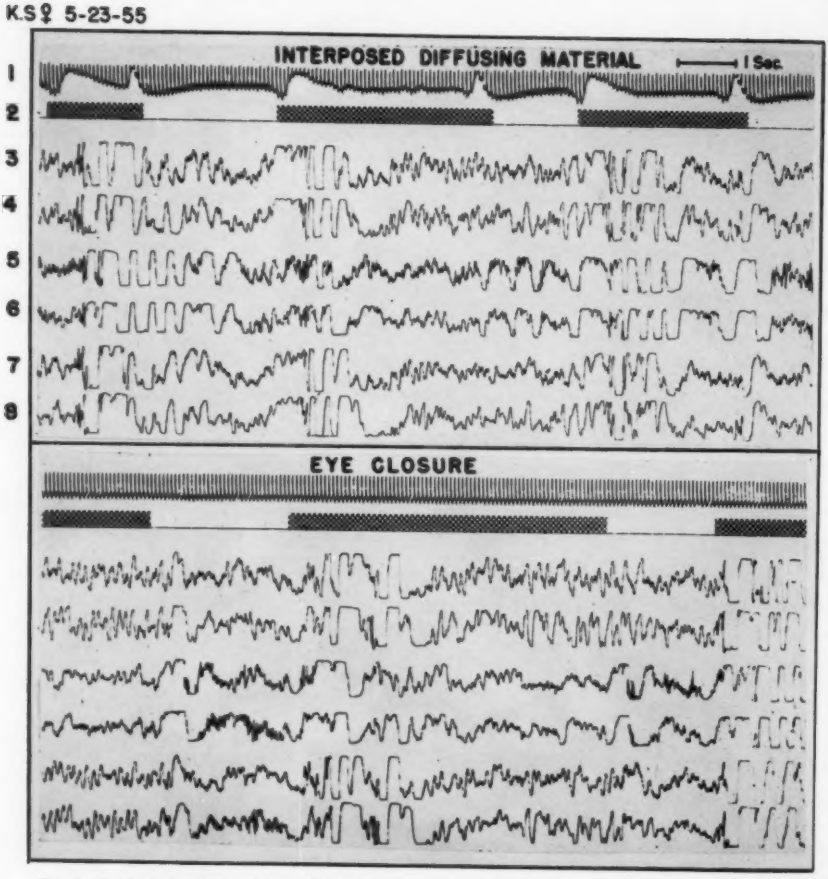

FIG. 3. Cerebral electrical activity of K. S. aged 4 years (case V 2 Family A) during continuous bilateral rhythmical retinal illumination with intermittent diffusion (upper panel) and during continuous flicker with intermittent eye closure (lower panel). The convention for lead derivations of figure 2 applies except for channel 2. Cross hatched bars in upper panel indicate interposition of diffusing material, in lower panel period of eye closure.

ing eye closure produced only a ca. 9 per second activity of good regularity without excessive augmentation of amplitude. This was bilateral, symmetrical, and synchronous, occurring in occipital-parietal regions, and quite consistent with normal alpha activity. With hyperventilation there was a gradual increase in slow activity beginning as an augmentation of amplitude of alpha gradually increasing locally in parietal and occipital regions and extending to involve the entire recording area with a dominant slow activity in a ca. 3 to 5 per second range. There were no abnormal evoked responses during the initial period of intermittent retinal illumination, but with each successive train of stimuli there occurred an evoked cerebral electrical abnormality precisely like that which has been described in detail for

the sister (case V 1 above). Eye closure during intermittent retinal illumination was particularly effective in precipitating the abnormal evoked response. Precipitation with interposed diffusion material was the same as for case V 1 and was particularly effective. There was no variation in susceptibility to evoked abnormality as a result of interposing clear gelatin filters red, blue, or green in color. Changes were related only to the presence of diffusion regardless of color.

Electroencephalographic findings. R. L., *Case* III 12: An eight electrode electroencephalogram made according to the technic described above showed no abnormalities in the resting trace nor during intermittent retinal illumination at various frequencies and intensities over a prolonged period of illumination. Impression: No abnormalities were observed in the electroencephalogram of this relative.

FAMILY B (figure 1)

Case III 2: S. M., a six year old white girl, was seen in the neurologic outpatient department because of a chief complaint of "behavior problem." The mother believed the patient was not normal because of fear of "high places," eating difficulties, and episodes when the patient appeared to be unaware of her environment. She occasionally fell forward suddenly without warning. There was no observed loss of consciousness.

The patient was born of a normal full-term spontaneous delivery with no complications. When she was first examined, the patient's father was 58 years old, the mother (H. W., case II 2) 37 years old, and one male sibling eight years old (J. M., case III 1). There was no known history of seizures in the patient's parents or grandparents.

At examination the patient was a shy, apprehensive girl who cooperated well. There were no abnormalities found on neurologic examination. Optic fundi were normal.

Laboratory findings showed that complete blood count, urinalysis, nonprotein nitrogen, and blood Micro-Hinton studies were normal.

Electroencephalographic findings. S. M., *Case* III 2: There was no definite abnormality during the resting tracing or during hyperventilation. There was very high relative amplitude slow activity throughout the entire recording area. During intermittent retinal illumination there was a high relative amplitude spike and slow wave discharge occurring initially as an harmonic of the stimulus frequency but becoming independent of it with the eventual development of multiple spike discharges followed by irregular slow waves, occasionally repeated rhythmically as spike and wave discharges of 3 cycle per second frequency distributed throughout the recording area. With the onset of intermittent trains of stimulation a symmetric myoclonic jerk occurred. Interpretation was that of an abnormal electroencephalogram because of marked alteration during hyperventilation and because of widespread symmetric multiple spike and slow wave discharges accompanied by myoclonic jerks on intermittent retinal illumination.

Electroencephalographic findings. H. W., *Case* II 2 (mother of S. M.): No abnormalities were observed in the resting record or during hyperventilation. During intermittent retinal illumination there occurred a gradually augmenting amplitude occipitoparietal response, initially an harmonic of stimulus frequency. There was, in addition, a superimposed electromyographic response which was shown by additional electrode application to arise from contraction of orbicularis oculi and frontalis superimposed in the most proximate leads. There was palpable and visible contraction of orbicularis oculi which increased in strength with successive flash stimuli. At such a time the patient experienced a subjective feeling of "falling." Interpretation was that of an abnormal electroencephalogram because of the changes which occurred during intermittent retinal illumination. The response is that which has been described as "photomyoclonic" by Bickford and co-workers[15] (figure 4).

Electroencephalographic findings. J. M., *Case* III 1: In the resting trace there was a very high relative amplitude discrete wave form fast activity of ca. 30 per second frequency of greatest prominence in the frontal and central regions primarily. No change of significance occurred during hyperventilation. During intermittent retinal illumination there was a very high relative amplitude occipital and parietal slow wave response, with an admixture of multiple spike discharges showing progressive augmentation of amplitude. These changes were precipitated with eye closure during intermittent retinal illumination. Interpretation was that of an abnormal electroencephalogram because

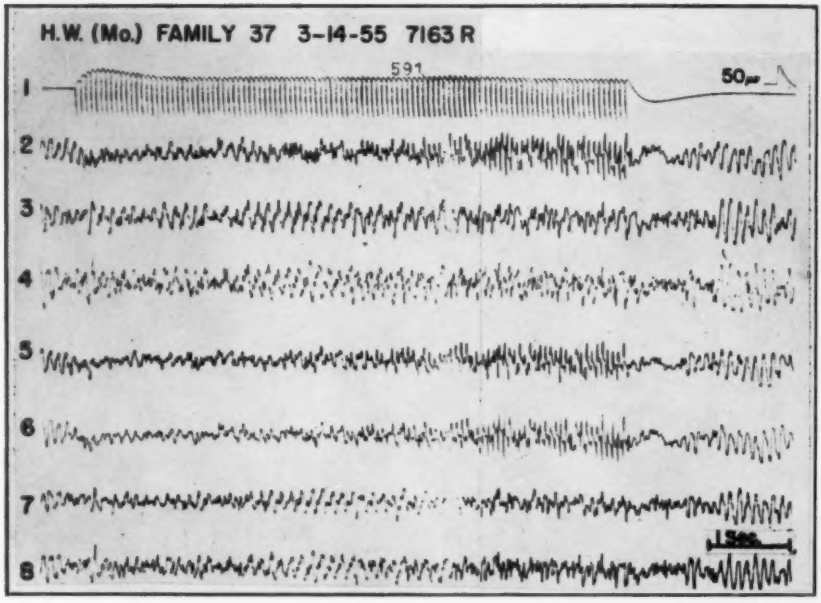

FIG. 4. Cerebral electrical activity (channels 3 to 8) of H. W. (case II 2 Family B—mother of case III 1 Family B) illustrating "photomyoclonic response" recorded during bilateral intermittent retinal illumination. The electromyographic recording derived from the right orbicularis muscle is recorded in channel 2. The photocell signal of flash stimulus is recorded in channel 1. Muscle contraction of electromyogram was superimposed as artefact in channels 5 and 6, which represent electrodes most proximate to the contracting orbicularis oculi muscles.

of the very high relative amplitude discrete wave form fast activity in the resting record and an abnormal response to intermittent retinal illumination consisting of polyspike and slow wave discharges of greatest prominence in occipital and parietal regions but spreading to central and frontal regions as well.

FAMILY C (figure 1)

Case III 2: R. D., a five and a half year old boy, was admitted to the Boston Floating Hospital on February 3, 1954 with a complaint of seizures occurring three weeks prior to admission. The child was born of a gypsy father. The mother was mentally deficient. He had one sister aged four years (J. D., case III 3) and another sibling whose whereabouts were unknown. There was no history of seizures in the parents or grandparents. The maternal grandmother was hospitalized in a state mental hospital where she committed suicide.

The patient did not walk until age three years and had only a limited vocabulary at that age. He has been described as a "nervous child." At the age of two years the patient suffered a head injury with no known sequelae.

Three weeks prior to admission the patient was observed to have twitching movements of both arms, "foaming at the mouth," and "rolling up" of both eyes. Both legs were sharply flexed on the abdomen. This is said to have lasted 15 minutes and was followed by 18 hours of unresponsiveness. On the day prior to admission he had a similar seizure, followed by several hours of unresponsiveness, disturbed behavior, and persistent vomiting.

General physical examination revealed a small, slender boy of dark complexion who was friendly and cooperative. Neurologic examination revealed normal orientation but amnesia

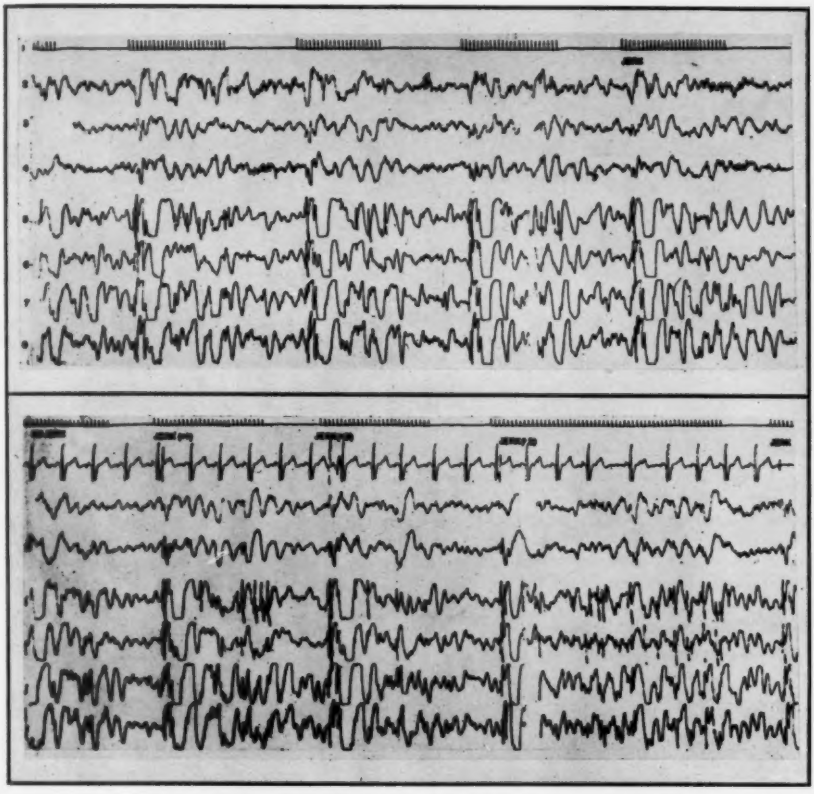

FIG. 5. Examples of the cerebral electrical activity of R. D. aged 5 years (case III 2 Family C) during intermittent bilateral retinal illumination. Consecutive channel numbering 1 through 8 applies to both panels according to the following convention: Channel 1. Photoelectric cell recording of individual flash stimuli or left frontotemporal. 2. Right frontal-temporal. 3. Left temporal-posterior temporal. 4. Right temporal-posterior temporal. 5. Left posterior temporal-occipital. 6. Right posterior temporal-occipital. 7. Left parietal-occipital. 8. Right parietal-occipital, with exception that channel 2 of the lower panel of this figure represents a bipolar electromyographic recording derived from the right pectoralis major. Electrocardiogram is derived from the same leads.

for the two episodes of seizure activity. He had difficulty remembering recent events, for example, whether or not he had been attending school. (He had been attending kindergarten regularly and doing satisfactorily.) There was no abnormal pigmentation of the retina. The macula was natural in apearance. The response to repeated painful stimulus of pinprick was that of continuous bursts of laughter.

Examination of blood, urine, and cerebrospinal fluid revealed no abnormalities. Chest and skull films were normal.

Electroencephalographic findings. R. D., *Case* III 2 (figure 5): Throughout the tracing there was a dominant, symmetric ca. 6 per second activity, of greatest relative prominence in occipital and parietal regions symmetrically and bilaterally. No definite abnormalities occurred in the resting tracing. During hyperventilation there was an increase in the amount of slow

activity, and after two minutes of hyperventilation there appeared a bilateral, symmetric, synchronous polyspike and slow wave discharge followed by slow activity in the ca. 3 per second range occurring rhythmically with progressively diminishing amplitude. During intermittent retinal illumination there was the type of evoked abnormality which corresponded with that described for case V 1, family A (see above). The abnormalities occurred at any stimulus frequency when intensity was sufficiently great. Intermittent trains of stimuli produced abnormal discharges of greatest relative prominence during the early portions of the stimulus train. There occurred bilaterally symmetric rhythmic contraction of the orbicularis oculi with superimposed electromyographic spike which was apparent in the nearest leads. As the intermittent trains of stimulus were repeated there were symmetric, synchronous, sudden jerks of the arms in flexion, adduction at shoulder, and flexion at elbow. These occurred in the same pattern but with increasing strength of contraction if the intermittent trains of stimuli were continued. If trains of stimuli were interrupted for a significant period of time the susceptibility to clinical manifestations in the form of myoclonic jerks was dissipated, being reestablished with resumption of intermittent trains of stimuli after a sufficient latency.

Electroencephalographic findings. J. D., *Case* III 3 (figure 6): In the resting tracing there was a dominant ca. 4 to 5 per second slow wave activity with an admixture of other frequencies. The slow activity was most prominent in occipital and parietal regions, symmetric, bilateral, and generally synchronous. There was in the frontal regions a bilateral symmetric, high relative amplitude discrete wave form ca. 30 per second activity of precisely the same type as that observed in the brother (case III 2, see above). During continuous intermittent retinal illumination (flicker), there was a gradual enhancement in the amplitude and areal involvement of the fast activity described. There was in addition the introduction of bilateral, symmetric, slow activity occurring in bursts and showing gradual progressive augmentation of amplitude. Eye closure or the interposition of diffusing material (white paper) with eyes closed had the effect of precipitating the abnormalities which in this record showed essentially the same morphologic features and area distribution as that described for her brother (case III 2). There occurred a rhythmic, palpable, bilateral, symmetric, and synchronous contraction of orbicularis oculi with each stimulus for long periods of stimulation. Symmetric, myoclonic jerks occurred with the initial flashes of intermittent stimulus trains presuming prior facilitation (see description for case III 2).

FAMILY D (figure 1)

Case II 1: K. C., a white male child of eight years, was referred to the Boston Dispensary neurology clinic on September 20, 1954 for evaluation of a right facial paralysis present since birth. The patient's mother, M. C., aged 34 (case I 1), had had repeated petit mal seizures over a period of at least ten years and two generalized convulsive seizures approximately two years ago. There was no history of seizures in the father or grandparents. Two siblings, a girl aged 12 years (E. C., case II 2) and a two year old boy were both asymptomatic. The patient was born of a normal full-term, spontaneous delivery and developed normally. A right facial palsy was noted at birth. The patient developed normally, sitting at four months, walking at nine months, and talking at one year. He had difficulty at school, especially in reading, because of continual hyperactive behavior and poor attention.

At examination the patient was a well developed, well nourished boy, somewhat shy, with little spontaneous activity or speech. There were no abnormalities on general physical examination. Neurologic examination revealed some slowness in cooperating with the examiner. There was a right peripheral facial palsy. Motor system examination revealed a slight weakness of the grip of the right hand and many sudden flexion extension movements of the fingers and hands bilaterally.

Psychometric testing (Wechsler Intelligence Scale) revealed an I.Q. within normal limits (91), with low general information and reasoning ability consistent with disturbed cerebral function.

Electroencephalographic findings. K. C., *Case* II 1: In the resting tracing there was scattered slow wave activity with no apparent asymmetry. During hyperventilation there was marked increase in slow activity with rhythmical ca. 2½ per second slow activity present throughout the entire recording area. No abnormalities oc-

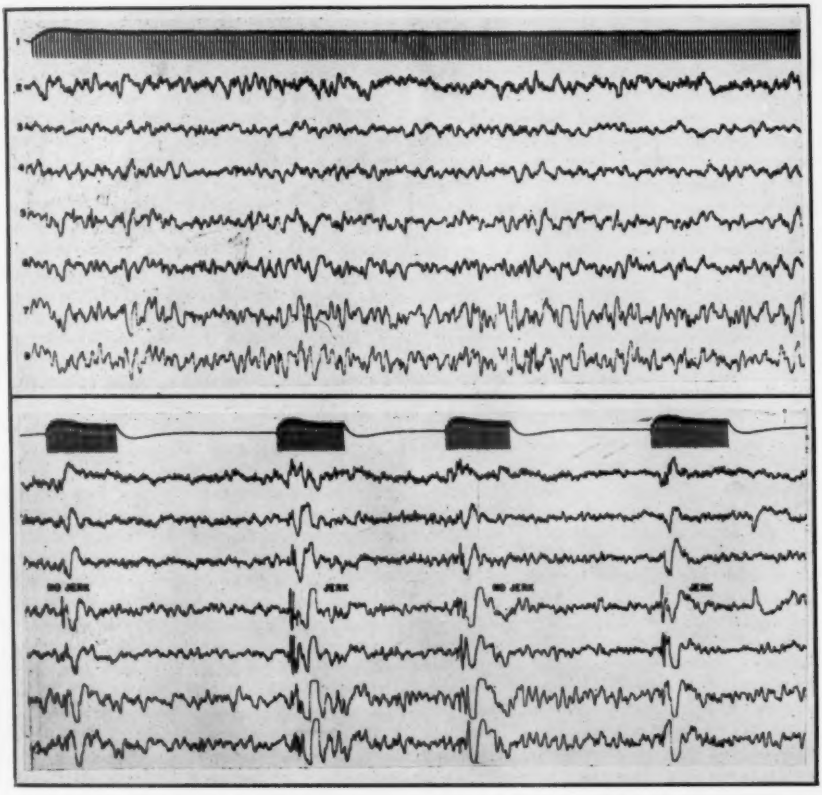

FIG. 6. Cerebral electrical activity of J. D. aged 4 years (case III 3 Family C—sister of R. D.). Recordings during bilateral intermittent retinal illumination. The convention described for figure 5 applies.

curred during intermittent retinal illumination in the early portion of the stimulation period. During the latter portion of stimulation period with intermittent trains there was an evoked bilateral synchronous polyphasic spike discharge with alternating slower frequencies throughout the entire recording area. The response to intermittent retinal illumination was considered abnormal.

Electroencephalographic findings. E. C., *Case* II 2: The resting tracing showed no abnormalities. During hyperventilation there was excessive slow activity. On one occasion during intermittent retinal illumination there was a paroxysmal discharge confined to occipital and parietal regions which bore no clear relation to stimulus in terms of the frequency response. Interpretation: Abnormal electroencephalogram because of changes occurring during hyperventilation; no positive abnormality due to intermittent retinal illumination.

Electroencephalographic findings. M. C., *Case* I 1: No abnormalities were seen in the resting tracing which had a quite regular alpha activity in occipital and parietal distribution. During hyperventilation there was a bilateral, symmetric, synchronous, rhythmic, alternating spike and wave discharge at ca. 3 per second

which occurred in bursts and runs of approximately three seconds duration distributed throughout the entire recording area. During intermittent retinal illumination no significant changes occurred during the first portion of the stimulation period. During the latter portion of the period of intermittent retinal illumination, with eyes closed, there was a regularly evoked cerebral occipital parietal response which corresponded to "normal photic driving" but showed progressive augmentation of amplitude and additional spike discharges from time to time. This record was interpreted as being abnormal during the period of hyperventilation, and showed changes during intermittent retinal illumination which were sufficiently unusual to be termed "probably abnormal."

FAMILY E (figure 7)

Case III 1: M. D., a white female child of 14 years was seen in December 1954 in neurologic consultation with the complaint of "spots before her eyes and unconsciousness." The patient had a normal, full-term delivery without neonatal complications. The mother (case II 2) was of borderline intelligence. She had six siblings, sisters aged 13 and 10, and brothers aged 11, six, three, and eight. A maternal aunt (case II 3) died at the age of one year after having "frequent convulsive seizures." Several maternal cousins have had febrile seizures (cases III 7, 8, and 9). Approximately one month prior to admission and on several occasions since that time the patient had had transient episodes during which she saw scattered small "red spots" before her eyes. Frequently, bilateral frontal headaches accompanied these episodes. She was asymptomatic between episodes. Approximately one week prior to admission the patient saw the "red spots" and immediately thereafter lost consciousness for approximately five minutes. She regained consciousness with no drowsiness or confusion. The child has been described as always having been "slow mentally" and since the third grade had been in special classes at school. At the time of examination she was in a special eighth grade class. There was no history of severe infectious diseases other than the usual childhood diseases. She had had no severe injuries.

On general physical examination the patient was well developed and well nourished with no abnormal physical findings. Neurologic examination revealed some limitation of general information and knowledge, as well as poor calculating and reading ability for a child this age. Examination of cranial nerves, motor, and sensory systems revealed no abnormalities.

Urinalysis, blood sugar, sedimentation rate, and complete blood count were all within normal limits. Skull films revealed no abnormalities.

Electroencephalographic findings. M. D., *Case* III 1: There was no abnormality in the resting tracing or during hyperventilation. During intermittent retinal illumination there was, during the first portion of the period of illumination, normal "photic driving." During the latter portion of the period of illumination there was, with each of intermittent stimuli, a very high relative amplitude rhythmic, primarily occipital-parietal slow wave discharge with multiple spikes superimposed in a harmonic of the stimulus frequency. These were of excessive relative amplitude as compared with observations in 615 controls. A tracing four months later showed at the end of the period of intermittent retinal illumination, during intermittent trains of stimuli, augmenting amplitude slow activity with superimposed spikes showing no relation to stimulus frequency and constituting an irregular, multiple spike and slow wave discharge. Stimulus was terminated in order to prevent the development of clinical symptomatology. The interpretation was that of an abnormal electroencephalogram because of slow wave and spike and slow wave discharge evoked during intermittent retinal illumination.

FAMILY F (figure 7)

Case III 1: H. D., a white single, high school student age 16 years, was seen in the neurologic outpatient department with a history of generalized seizures in the three year period prior to admission. The patient was an only child and there was no history of seizures in his parents or his grandparents. His mother (case II 3) had had occasional episodes of "lightheadedness" without loss of consciousness. A maternal cousin (case III 2) had generalized seizures and a paternal uncle (case II 1) suffered from recurrent enuresis into adult life. The patient developed normally from birth with no known serious illnesses or injuries. His first seizure occurred in 1952 when he suddenly lost consciousness without warning, with postictal drowsiness of two hours' dura-

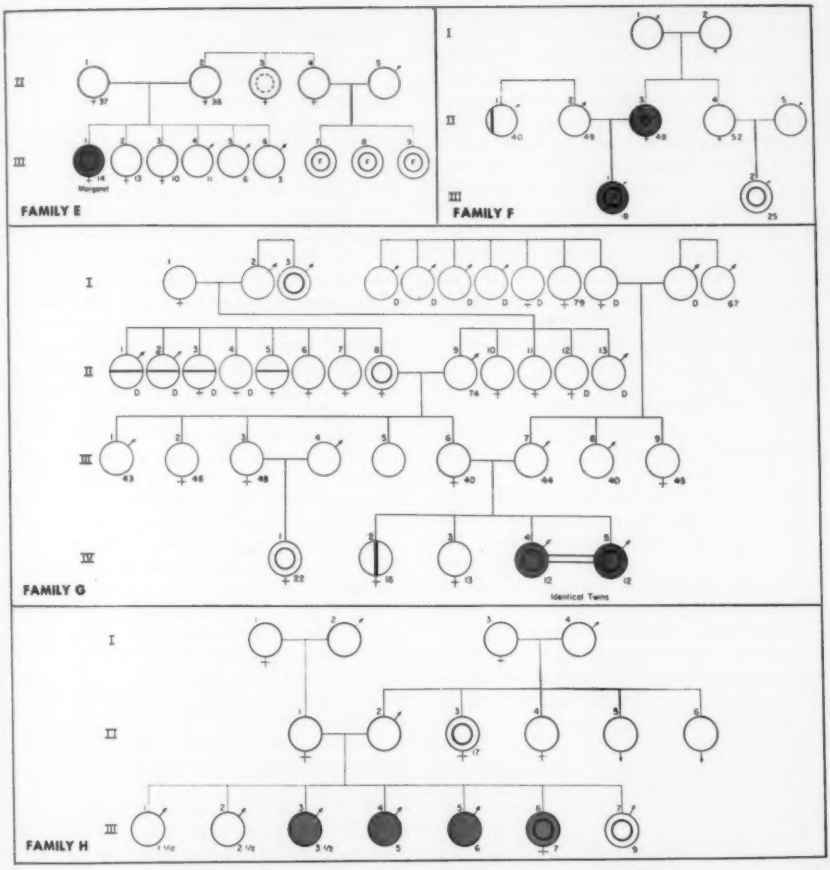

FIG. 7. Pedigrees of families E, F, G, and H. For convention see legend to figure 1.

tion. In the past year he had had two generalized seizures, one preceded by a feeling of "blood rushing to my head."

General physical examination revealed frequent extrasystoles, a split first sound at the apex, and a soft systolic murmur. There was smallness of bone structure of left face but no asymmetry of trunk or extremities. Neurologic examination revealed no abnormalities.

Hemogram, urinalysis, sedimentation rate, blood Hinton, and Kahn studies were normal. Chest and skull roentgenograms were normal, and an electrocardiogram was normal.

Electroencephalographic findings. H. D., *Case* III 1: No abnormality occurred in the resting tracing. During intermittent retinal illumination a very high relative amplitude burst of slow activity appeared in all leads. It bore no relation to flicker frequency. At the time of the electroencephalographic discharge the patient "felt funny." Interpretation was that of an abnormal tracing because of excessive widespread evoked abnormality during intermittent retinal illumination.

Electroencephalographic findings. L. D., *Case* II 3: No abnormality occurred during the resting tracing. During intermittent retinal illumination there was progressive enhancement of the evoked occipital and parietal response which, with eyes closed, was consistent with normal "photic driving" until the latter portion of one of the interrupted stimulus trains when there occurred multiple spike discharges of excessive relative amplitude. At this time the mother stated that she had a "feeling." This feeling was repeated several times, during each of which there was an excessive response in occipital and parietal regions. The response during intermittent retinal illumination was interpreted as "probably abnormal."

FAMILY G (figure 7)

Case IV 4 and *Case* IV 5: A. C. and J. C., 12 year old identical male twins with seizures, were examined at the suggestion of Dr. William G. Lennox. There was no history of seizures in the parents; however, the maternal grandmother (case II 8) had convulsive seizures and a maternal great-grand uncle (case I 3) had generalized seizures. A female sibling (case IV 2) aged 16 years is reported to have an electroencephalographic abnormality consistent with petit mal. A maternal cousin aged 22 (case IV 1) had a history of generalized seizures. At present both boys have been free of major and minor seizures for three years. They first had seizures at the age of approximately three years.

Physical and neurologic examinations revealed no abnormalities. Optic fundi were normal.

Electroencephalographic findings. A. C., *Case* IV 4: During intermittent retinal illumination there appeared, after a latency in occipital and parietal regions with each of intermittent trains of stimuli, a very high relative amplitude paroxysmal slow wave discharge. Each was accompanied and preceded by a spike discharge.

Electroencephalographic findings. J. C., *Case* IV 5: The changes occurring during intermittent retinal illumination in this record were the same as those described for the record of his identical twin (case IV 4). The record was abnormal because of evoked spike and slow wave responses from occipital and parietal cortex during intermittent retinal illumination.

FAMILY H (figure 7)

Case III 6: G. S., a white school girl of seven years, was first seen in May 1954 with a history of seizures which the patient had first experienced at the age of four years and for a two year period thereafter. Generalized seizures had occurred with sudden falling, loss of consciousness, and "foaming at the mouth." There was no tongue-biting or incontinence. These seizures occurred as often as three or four times a day. There was no known sensitivity to light or sound. The patient frequently demonstrated transient episodes when she was unresponsive to any stimulus but did not fall. The patient had a normal full-term spontaneous delivery with no prenatal or neonatal complications. There was no history of seizures in the patient's parents or grandparents; however, a paternal aunt aged 17 (case II 3) experienced generalized convulsions at the age of 12 years. The patient has six siblings ranging in age from nine years to 13 months. S. S., aged nine (case III 7), had generalized convulsive seizures as often as three to four times a day from the ages of two to four years, but she has had none since then and requires no medication. The patient has been "slow" in school since the second grade and has been attending special classes. Martin, aged three and a half (case III 3), is mentally retarded at this time. He began walking and talking using only short phrases at the age of three years. Allen, aged five (case III 4), was also tested during this investigation. None of the children had any known complications at birth, serious infections, or trauma.

On neurologic examination the patient was phlegmatic and responded slowly and without initiative but with good cooperation. She was of low normal intelligence. Examination of cranial nerves and motor and sensory systems revealed no abnormalities.

Electroencephalographic findings. A. S., *Case* III 4: There was no positive abnormality in the resting tracing. No change of significance occurred during hyperventilation. During intermittent retinal illumination there was, in the latter portion of the period of illumination, with each intermittent stimulus train, appearing throughout the entire recording area simultaneously and symmetrically, a multiple spike discharge followed by slow activity. Interpretation was that of an abnormal electroencephalogram

because of evoked multiple spike and slow wave changes during intermittent retinal illumination.

Electroencephalographic findings. G. S., *Case* III 6: There was in the resting tracing scattered slow activity with slight "build-up" during hyperventilation. During the long period of intermittent retinal illumination there was a gradually increasing incidence of evoked abnormal discharges which were most prominent in the occipital and parietal regions but also present throughout the remainder of the recording area simultaneously, taking the form of bilateral, symmetric multiple spike and slow wave discharges. Interpretation was that of an abnormal electroencephalogram because of abnormal evoked response during intermittent retinal illumination.

Electroencephalographic findings. M. S., *Case* III 3: No definite abnormalities were observed in the resting tracing. During intermittent retinal illumination there was a gradual augmentation of amplitude of slow activity in the ca. 7 per second range, with rather marked slowing which occurred bilaterally and symmetrically with greatest relative prominence in occipital and parietal regions but present throughout the entire recording area. This stopped with cessation of intermittent retinal illumination and was resumed with resumption of stimulus. Interpretation was that of an abnormal electroencephalogram because of excessive amplitude evoked response during intermittent retinal illumination.

FAMILY I (figure 8)

Case II 2: W. W., a white married fireman aged 31 years, was first seen in neurologic consultation in 1950 with a complaint of "black-out spells" and "fluttering of eyelids." The patient had a two year history of repeated episodes of "blinking of eyelids" and "fogginess" in thinking. His electroencephalogram at another hospital had been reported as normal at that time. These episodes were transient, occasionally terminating with turning of the head and eyes to one side. On a few occasions he lost consciousness at that point and was observed to have clonic movements of the extremities and falling, with postictal confusion and drowsiness.

The patient was seen again in February 1955 with a complaint of continued episodes of "interference with his thinking," associated with fluttering of his eyelids and "black-out spells." There was no history of seizures in parents or grandparents. Four siblings have been free of seizures. The patient has four children, all girls, one aged two years (J. W., case III 1), another aged four (C. W., case III 4), and two others aged five and one and a fourth years. None of the children have had seizures, infections, or traumata of the central nervous system.

The patient stated that he had seizures only during the daytime and then only when exposed to direct sunlight. Prior to the seizures he experienced an uncontrollable, involuntary fluttering of his eyelids or the passing of his right hand before his eyes rapidly back and forth. He was unable to control this movement and a seizure always follows the interruption of the light by the moving hand. There was also an element of pleasurable sensation, or "release of tension" and satisfaction associated with this movement and the subsequent seizure. He never had a seizure in reflected sunlight or artificial light. The seizures usually occurred in the morning between 8 and 8:30 when the sun is low. He is aware of the blinking of his eyes or the moving of his hands, and in spite of conscious efforts to stop it, the eyes begin blinking again, or the hand rises rapidly to pass back and forth before the eyes again.

General physical and neurologic examination revealed no abnormalities. Routine blood and urine studies were normal.

Electroencephalographic findings. W. W., *Case* II 2: There were no abnormalities observed during the resting tracing and none during hyperventilation. During intermittent retinal illumination there occurred no change initially in the early period of illumination, but subsequently regardless of frequency or intensity there appeared a very high, gradually augmenting amplitude spike and wave discharge present in occipital, parietal, central, frontal, and temporal regions. Occasionally there occurred multiple spike discharges of gradually augmenting amplitude followed by slow activity. At subliminal intensity and frequency interposition of a diffusion material between light source and patient was sufficient to precipitate the abnormality. It was evident, however, that intensity was the prepotent parameter of adequate stimulus and with reduction of intensity by dark glasses the response could be prevented for very high intensity illumination.

Electroencephalographic findings. C. W., *Case* III 4: There was in the resting tracing a very high relative amplitude discrete wave form ca. 30 per second activity which was of greatest relative prominence in parietal regions. There were in addition bursts of high relative amplitude slow activity in the ca. 3 per second frequency range occurring primarily in the same region. The slow activity was precipitated by closing the eyes and disappeared with opening of the eyes. During intermittent retinal illumination there was, during long periods of illumination, a gradual augmentation of amplitude of the slow activity which was of sharp slow wave form ca. 4 per second in frequency and alternating with faster frequencies to form a very blunt "spike wave" discharge. Interpretation was that of an abnormal electroencephalogram, because of the discrete wave form, high relative amplitude fast activity, and the precipitation of slow activity with eye closure during the resting tracing and because of gradual augmentation of slow activity during intermittent retinal illumination.

Electroencephalographic findings. J. W., *Case* III 1: No abnormalities were noted in the resting tracing, considering the age of the subject (two years). During intermittent retinal illumination there was a gradual enhancement of amplitude with the appearance of sharp wave forms and multiple spike discharges of excessive relative amplitude. This was most prominent in occipital and parietal distribution. Interpretation was that of an abnormal electroencephalogram because of evoked spikes and augmented amplitude slow activity during intermittent retinal illumination.

FAMILY J (figure 8)

Case III 2: A. P., a white single school girl aged 16 years, was seen in neurologic consultation on two occasions, the first time in 1949 and the second in 1952, with complaints of "spells" since the age of five or six years. The patient's mother, F. P., aged 34 (case II 2), had had momentary transient dizzy spells without loss of consciousness since childhood. She had a history of hemicephalalgia of many years' duration, each preceded by a sensation "as if her eyeballs were being drawn out through her eyelids." There was no history of seizures in the mother, father, or grandparents. There were two younger siblings. A male, A. P., aged 12 (case III 1), has had severe hemicephalalgia since the age of seven associated with nausea and vomiting. He has been in special classes at school. A female, aged seven, has multiple congenital abnormalities, including bilateral club feet, ptosis, and torticollis. The patient had frequent episodes of "petit mal" from the age of six to ten years, then began to have both minor and major convulsive seizures.

General physical and neurologic examination revealed a well developed and well nourished girl with no abnormalities.

Routine blood and urine studies, blood chemistry, and chest and skull films were normal. Cerebrospinal fluid examination revealed no abnormalities. Psychometric testing of cases III 1 and III 2 revealed normal intellectual function.

Electroencephalographic findings. A. P., *Case* III 2: After a prolonged period of intermittent retinal illumination there occurred a bilateral, symmetric, high relative amplitude, multiple spike discharge with the quite rapid development of alternating spike and wave discharges of ca. 3 per second frequency. These occurred with eye closure during intermittent retinal illumination. Interpretation was that of an abnormal electroencephalogram because of evoked spike and wave discharges during intermittent retinal illumination.

Electroencephalographic findings. A. P., *Case* III 1: During intermittent retinal illumination with double flashes there occurred a high relative amplitude spike and slow wave discharge of variable frequency occurring in bursts and runs appearing throughout the entire recording area simultaneously and symmetrically. Interpretation was that of an abnormal electroencephalogram because of spike and wave discharge occurring during intermittent retinal illumination.

Electroencephalographic findings. F. P., *Case* II 2: There occurred during intermittent retinal illumination a rhythmical slow activity which was an harmonic of the flicker frequency. It appeared throughout the entire recording area. This persisted beyond the cessation of illumination, and when stimulus was prolonged there occurred a subjective feeling which the patient identified at the time of each maximal response.

There occurred sudden contraction of orbicularis oculi with each flicker after prior facilitation. Interpretation was that of a probably abnormal electroencephalogram because of the

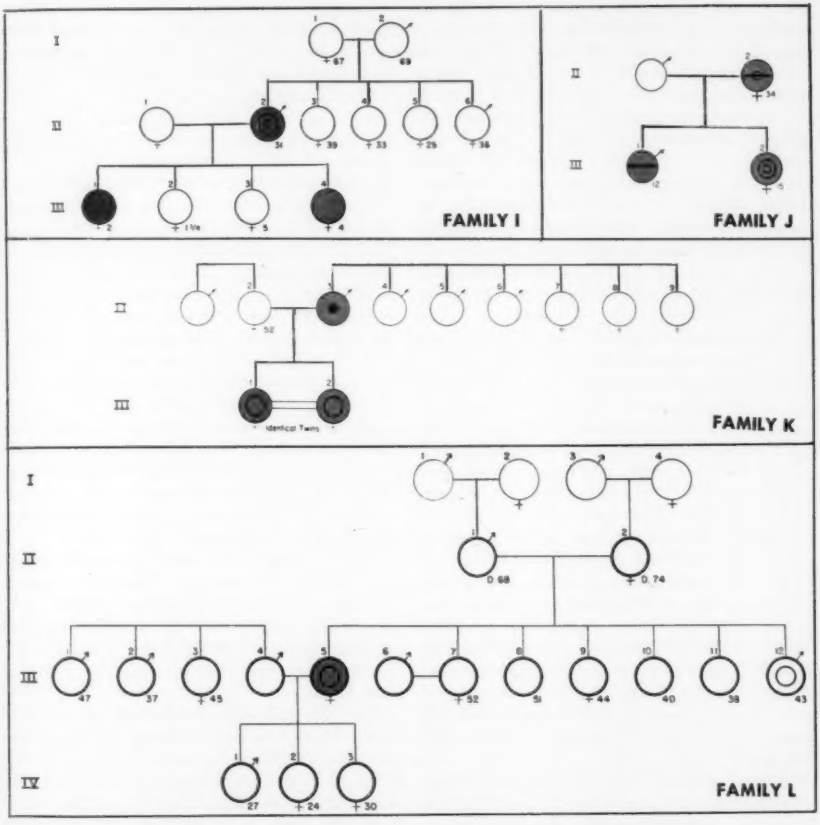

FIG. 8. Pedigrees of families I, J, K, and L. The convention of figure 1 applies.

findings described which are consistent with the so-called "photomyoclonic response."

FAMILY K (figure 8)

Cases III 1 and III 2: N. C. and B. C., 21 year old identical female twins each of whom have had seizures, were studied at the suggestion of Dr. William G. Lennox. They are part of Dr. Lennox's series of twin pairs.[24] Each of the twins has had both "grand mal" and "psychomotor seizures" since the age of 13 years. They had normal full-term spontaneous deliveries with no history of birth trauma, severe infections, or injuries after birth. There was no history of seizures in the parents or grandparents. The twins have been free of seizures for four years. The patient's father, J. C., aged 48 (case II 3), had no history of any convulsive disorder.

General physical and neurologic examination revealed no abnormalities.

Electroencephalographic findings. N. C., *Case* III 1: No abnormalities were observed in the resting tracing or during hyperventilation. During intermittent retinal illumination there occurred during the latter portion a burst of very rapid alternating spike and wave discharges of ca. 6 per second frequency for each complex.

These were uniformly precipitated by closure of the eyes during intermittent retinal illumination. It did not occur with closure of the eyes without retinal illumination. Multiple spike discharges usually alternating, however, with the slow activity to form a rapid "spike-wave" complex was the rule. The discharge was primarily apparent in occipital and parietal regions but on occasion occurred bilaterally, symmetrically, and simultaneously throughout the entire recording area. Interpretation was that of an abnormal electroencephalogram because of a rapid "spike-wave" discharge evoked upon eye closure during intermittent retinal illumination.

Electroencephalographic findings. B. C., *Case* III 2 (identical twin of case III 1): No abnormalities were observed during the resting tracing or during hyperventilation. During intermittent retinal illumination there occurred with gradually increasing facility as illumination proceeded occipital and parietal paroxysmal slow wave discharges alternating with high relative amplitude spike discharges as described for case III 1. In addition there was a superimposed electromyographic "spike" which was present in the frontal regions as well as the occipital. This latter type of discharge is consistent in its form and distribution with the so-called "photomyoclonic response." Interpretation was that of an abnormal electroencephalogram because of paroxysmal spike and slow wave evoked discharges in occipital and parietal regions during intermittent retinal illumination.

Electroencephalographic findings. J. C., *Case* II 3: No abnormalities were observed during the resting tracing or during hyperventilation. During intermittent retinal illumination there was a rather prominent "photic driving." During the latter portion of the period of illumination there occurred rapid enhancement of amplitude of the occipital and parietal evoked discharges which progressed with augmenting amplitude and the appearance of multiple spike discharges following cessation of illumination, immediately after which there occurred a generalized convulsive seizure for which the patient had no memory.

FAMILY L (figure 8)

Case III 5: A. B., a married woman of 48 years, was seen in October 1954 with a complaint of "blackout spells," headache, and posterior neck pain since August 1954. The patient admitted to "passing out" several times as a girl. There was no history of seizures in her parents or grandparents. One brother (case III 12), had a history of several generalized seizures. Two children aged 28 and 24 years were asymptomatic. After approximately two years of low back pain with radiation into the right leg, the patient had a lumbar myelogram and operation at another hospital in August 1954 for removal of a herniated intervertebral disk. Following myelography the patient developed headache and posterior neck pain which has persisted since. She had had recurrent episodes of unconsciousness since that time. These episodes were very brief; occasionally she falls but does not hurt herself. She had had no tongue biting or incontinence and only poorly described movements of the arms have been observed. Lumbar puncture was done one month following myelography and revealed 451 white blood cells, 75 per cent of which were lymphocytes; total protein was 256 mg. per cent. Smear and culture of the cerebrospinal fluid were negative.

General physical and neurologic examinations revealed no abnormalities. Lumbar puncture revealed clear fluid with normal pressure and dynamics. There were 57 lymphocytes, six polymorphonuclear leukocytes, and one red blood cell. Total protein was 105 mg. per cent. Sugar was 67 mg. per cent.

Electroencephalographic findings. A. B., *Case* III 5: There was in the resting tracing a dominant symmetric ca. 9 per second alpha activity in occipital and parietal distribution. This was quite regular. No changes of clinical significance occurred during the resting tracing or during hyperventilation. During intermittent retinal illumination there occurred evoked cerebral occipital and parietal responses correctly described as "photic driving," with a faithful following of stimulus rate for short periods. There then occurred slower evoked potentials of gradually increasing relative amplitude appearing at first as harmonics of the stimulus rhythm. There was eventually established an independence of the stimulus rhythm with slight discharge persisting after the cessation of stimulus. During the evoked abnormal response the patient experienced the aura which has preceded her "blackouts." Responses were bilateral, symmetric, and synchronous; they remained generally confined to occipital and parietal regions. They

were chiefly characterized, however, by a gradual augmentation of amplitude with the appearance of harmonics which with preceding spikes take the form of small "spike-wave" discharges.

FAMILY M (figure 9)

Case III 4: J. R., a single white female of 18 years was seen in neurologic consultation on March 22, 1955 with a complaint of "spells" occurring twice during the three months prior to admission. The patient had been entirely well with no known complications at birth and no severe infections or trauma since that time. She had a tonsillectomy in 1945 with no complications. There was no history of seizures in the mother (I. R., case II 2). However, the father, who died at the age of 41, had a history of several "black-out spells" and died suddenly with "bloody" cerebrospinal fluid. There was no history of seizures in the grandparents. One female sibling died of severe burns at the age of 7. Of the two remaining siblings, both girls aged 19 and 21, the older (J. R., case III 1) had a history of having had two generalized seizures at age eight years.

The patient had her first generalized convulsive seizure following an aura of "colored flashing lights" three months prior to admission. She suddenly lost consciousness and was observed to have a generalized seizure with tongue-biting. She had postictal confusion, amnesia, and drowsiness. She was well thereafter until four days prior to examination when, after a transient sensation of "floating away," she had another generalized seizure with tongue-biting and again postictal confusion, drowsiness, and amnesia.

General physical and neurologic examination revealed no abnormalities. Hemogram, blood sedimentation rate, urinalysis, fasting blood sugar, and two hour postprandial blood sugar determinations were normal. Serologic test for syphilis was normal. Cerebrospinal fluid examination was normal. Skull films and chest films were normal.

Electroencephalographic findings. J. R., *Case* III 4: There was no abnormality in the resting tracing. During hyperventilation there was an increase in the amount of slow activity which occurred in bursts of rhythmically repeated slow waves at ca. 3 per second. There was occasional alternating fast or slow activity with the production of a blunt "spike-wave." No changes of significance occurred during the early periods of intermittent retinal illumination, with interrupted trains of stimulus at various frequencies. In the later portion of the period of stimulation there appeared during prolonged stimulus trains slow activity in the occipital and parietal regions, and in addition in the frontal regions with bilateral symmetry and synchrony throughout the entire recording area. This was slow activity which showed a gradual increase in amplitude during the bursts and runs and a progressive slowing of successive waves. When such a burst was evoked it clearly persisted beyond the cessation of the stimulus train. Interpretation was that of an abnormal electroencephalogram during intermittent retinal illumination and probable abnormalities occurring during hyperventilation, age considered.

Electroencephalographic findings. I. R., *Case* II 2: The resting tracing and that recorded during hyperventilation showed no abnormalities. There was an evoked cortical response of the type described as "normal photic driving" occurring during the early period of illumination. During the latter period of illumination there occurred harmonics of stimulus frequency and alternating spike and wave discharges which showed progressive augmentation of amplitude but with greatest prominence in occipital and parietal regions. Interpretation: The response during intermittent retinal illumination was regarded as abnormal.

Electroencephalographic findings. J. R., *Case* III 1: There were no abnormalities in the resting tracing during hyperventilation or during intermittent retinal illumination (note history of generalized seizures at age eight years).

FAMILY N (figure 9)

Case III 1: W. S., a white male child of seven and a half years, was seen in the neurologic outpatient department in February 1955 because of the complaint of one generalized seizure occurring one night prior to admission. The patient's mother, father, and grandparents had no history of seizures. The father died at the age of 40, with a history of rheumatic fever as a child. A paternal uncle (case II 1) is reported to have had seizures as a child. The patient's siblings include one brother aged 11 and three sisters aged six (R. S., case III 3), four years, and three months of age. The patient was born of a normal, full-term cesarean

delivery at 6 pounds 13 ounces, with no jaundice or neonatal complications. He developed normally and had only the usual childhood diseases except for one episode of jaundice at the age of six.

On the night prior to admission the patient complained of a generalized headache after playing vigorously. He received some aspirin and went to bed feeling drowsy and "feverish." After sleeping for approximately four hours, he was observed to have a generalized convulsion with "choking noises," foaming at the mouth, and eyes rolling up in his head, with cyanosis and unresponsiveness. He was incontinent of urine. There was no history of febrile convulsions or significant head trauma.

General physical and neurologic examination revealed no abnormalities. Hemogram, urinalysis, blood sedimentation rate, and Hinton determinations were all normal. Skull films revealed no abnormality.

Electroencephalographic findings. R. S., *Case* III 3: There was scattered sharp wave and slow wave activity in the resting tracing, but no clear abnormality. No change of clinical significance occurred during hyperventilation. During intermittent retinal illumination there was good "photic driving" which was confined to the occipital and parietal regions, showing no abnormal recruitment or after-discharge until the latter portions of the period of intermittent retinal illumination when, with interrupted trains of paired flash stimuli, there were multiple spike discharges which appeared first in occipital and parietal regions and following each of which there was mixed slow activity of very high relative amplitude in the ca. 3 per second frequency range. The slow activity of 1/4 to 1/2 per second persisted in gradually diminishing amplitude for the succeeding three or four seconds. The multiple spike activity appeared in frontal and central regions as well but to a lesser degree. The interpretation was that of an abnormal evoked discharge during intermittent retinal illumination.

Electroencephalographic findings. W. S., *Case* III 1: No abnormalities were observed in the resting record. During hyperventilation there was a marked degree of "breakdown," with extreme relative amplitude slow activity throughout the entire recording area in the 1/2 to 3 per second frequency range. During intermittent retinal illumination there occurred high relative amplitude polyspike and slow wave discharges which were bilateral, symmetric, and synchronous. These were of the greatest relative amplitude and temporal primacy in occipital and parietal regions. Interpretation was that of an abnormal electroencephalogram because of the changes which occurred during hyperventilation and the abnormally evoked response during intermittent retinal illumination.

FAMILY O (figure 9)

Case IV 5: M. D., a white female child of two years, had been seen on three occasions in neurologic consultation since January 1954 because of the complaint of generalized convulsive seizures. On all three occasions the patient was seen because of generalized convulsive seizures with tongue biting and incontinence associated with temperatures ranging from 103 to 105° F. during an acute respiratory infection. The patient was born of a normal full-term spontaneous delivery with no neonatal complications and normal development to the present time. She first had seizures at the age of one year and persistently has had generalized convulsions with temperature elevations. There was no history of severe infection or trauma of the central nervous system. The patient's mother, L. D., aged 31 years (case III 4), had a history of generalized seizures from the age of two and one half to six years. She has had cataplexy and narcolepsy. She has sudden episodes of weakness associated with unexpected sounds or emotional outbursts and has episodes of uncontrollable sleep. The father, aged 31 years, had no history of seizures. There was no history of seizure disorder in the grandparents. The maternal grandmother (M. O., case I 12) was examined during this study and found to be light sensitive. A maternal uncle (case III 5) had a history of having had generalized seizures as a child.

General physical and neurologic examinations revealed no abnormalities. Routine blood and urine examinations were within normal limits. Spinal fluid examination revealed no abnormalities.

Electroencephalographic findings. M. O., *Case* I 12: There were no abnormalities during the resting record nor during the preliminary period of intermittent retinal illumination. During the latter portion of intermittent retinal illumination there occurred with each stimulus train a progressive augmentation of amplitude and the appearance of multiple spikes and slow

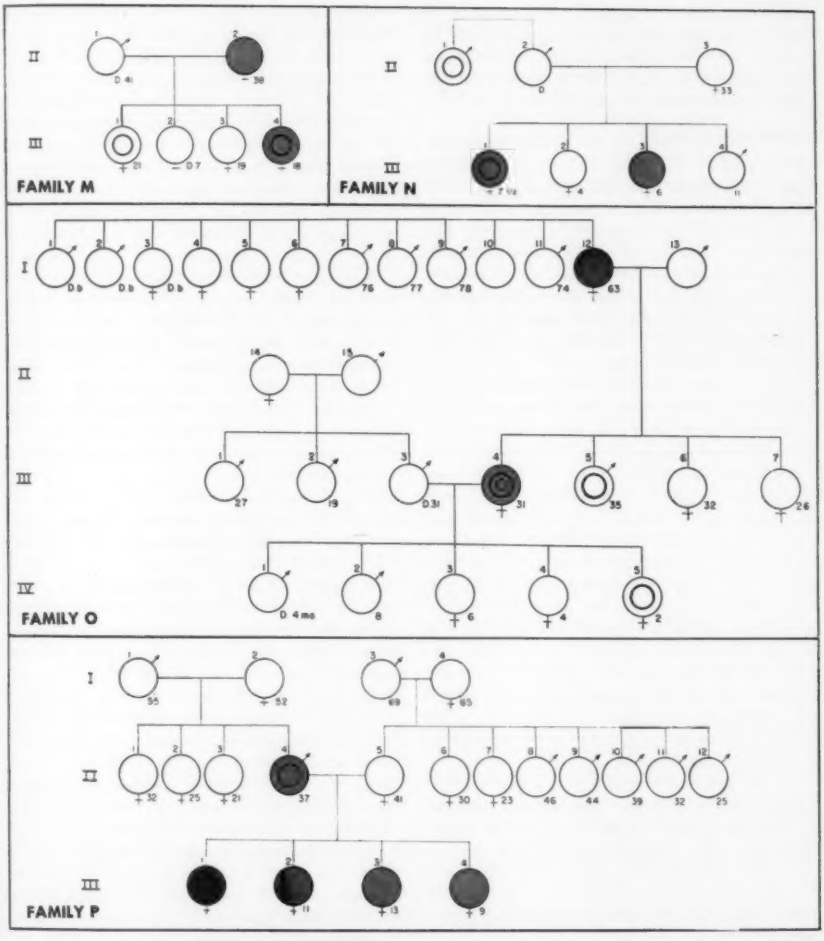

FIG. 9. Pedigrees of families M, N, O, and P. The convention of figure 1 applies.

wave discharges which, while of greatest prominence in the occipital and parietal regions, were also present more anteriorly. The interpretation was that of an abnormal evoked response to intermittent retinal illumination.

Electroencephalographic findings. L. D., *Case* III 4: No abnormality was observed during the resting tracing nor during the period of hyperventilation. During intermittent retinal illumination there was evoked slow activity of high relative amplitude in occipital and parietal distribution clearly in response to intermittent retinal illumination but bearing no relation to the frequency of stimulus. The evoked slow activity was in the 1/2 to 3 per second frequency range and included 14 per second bilaterally symmetric occipital "sleep spindles." During these episodes of illumination the pa-

tient was clinically asleep. Interpretation was that of an abnormal electroencephalogram because of the precipitation of the cerebral electrical changes associated with sleep as the result of intermittent retinal illumination.

FAMILY P (figure 9)

Case III 1: D. M., a white female of five and a half years, was first seen in April 1955 in neurologic consultation because of a history of generalized seizures occurring over the past four years. The patient had a normal full-term spontaneous delivery. She developed normally until about the age of one year when she was able to walk and say single words. The patient's mother is 41. The father, E. M. (case II 4), 37, had "fainting spells." There were three siblings, all females, B. M. aged 13 (case III 3), M. J. M. aged 11 (case III 2), and C. M. aged nine (case III 4). There was no history of seizures, severe infection, or trauma of the central nervous system in any of the siblings. There was no history of seizures in the parents or grandparents. The patient had chicken pox, measles, and pneumonia with temperatures to 105° F. rectally from the age of 14 months to 18 months with no seizures. During the next two years of life she had repeated seizures associated with temperature elevations to 102 to 105° F. rectally. During the past year she had had generalized convulsions two to five times a day. These frequently were preceded by a sense of "heat in her head" and visible flushing of the face. She had been incontinent of urine on one occasion.

At the age of about two years, after an episode of pneumonia with no seizures, the patient's mother stated that the patient's vocabulary deteriorated and since that time she has only been able to name members of her family or repeat radio and television commercials. She is believed to be able to understand orders and requests.

The patient was a small, well developed young female. Speech was unintelligible because of dysarthria. On neurologic examination the patient was quite hyperactive, moving about restlessly and kissing everyone indiscriminantly. She understood requests but responded poorly. There was slight left facial weakness of supranuclear type. Left ankle jerk was more active than the right; left plantar response was extensor.

Routine blood and urine examinations were normal. Blood Hinton was negative. Spinal fluid examination revealed no abnormality. X-rays of the skull and chest were normal.

Electroencephalographic findings. E. M., *Case* II 4: The resting tracing showed no abnormalities. No change of clinical significance occurred during hyperventilation. During intermittent retinal illumination lower frequencies evoked clinical responses of the type which may be described as "normal photic driving." There soon appeared, however, during intermittent trains of stimuli during the periods of illumination, high relative amplitude discrete wave form ca. 25 per second activity bilaterally and symmetrically in the occipital regions. There was in addition an evoked response at an harmonic of stimulus frequency (ca. 1/4 the stimulus rate). There also occurred high relative amplitude rhythmical spike discharges in addition to the normally evoked cortical response. These were confined to the occipital parietal region. The record was regarded as showing abnormal cerebral occipital and parietal responses to intermittent retinal illumination.

Electroencephalographic findings. B. M., *Case* III 3: There was in the resting tracing some slow activity in the 3 to 5 per second frequency range which was most prominent in occipital and parietal regions, in addition to the dominant alpha rhythm. No change of clinical significance occurred during hyperventilation. During intermittent retinal illumination there was a very prominent evoked cortical response faithfully following stimulus rate showing no evidence of progressive augmentation of amplitude; no evidence was seen of persistence beyond the cessation of stimulus during the early periods of illumination. After prolonged illumination there occurred bilateral symmetric variable sharp wave and spike responses showing progressive augmentation of amplitude. It occurred in occipital and parietal regions and briefly in temporal regions as well. The response to intermittent retinal illumination was considered to be abnormal. During initial periods of illumination the "photic driving response" was not regarded as abnormal.

Electroencephalographic findings. M. J. M., *Case* III 2: The resting tracing was normal. No change of clinical significance occurred during hyperventilation. The initial responses to intermittent retinal illumination were those of normal "photic driving." With repetition of stimulus, particularly stimulus trains, there oc-

curred high relative amplitude, arhythmical spike and slow wave discharges which were initially confined to occipital and parietal regions. High relative amplitude slow activity confined to the occipital and parietal regions with persistence of the evoked slow activity beyond a cessation of illumination and mixed with single and multiple spikes was seen repeatedly during the latter portions of the period of illumination. After prior facilitation the response to intermittent retinal illumination was abnormal.

Electroencephalographic findings. D. M., *Case* III 1: In the resting tracing there was scattered slow activity with intermittent accentuation of arrhythmical ca. 6 per second frontal and central rhythm. During the latter portion of the period of intermittent retinal illumination, there occurred high relative amplitude slow activity with superimposed fast activity of discrete wave form in the ca. 30 per second frequency range. The slow activity was, at this point, confined to occipital and parietal regions and occurred as an harmonic of stimulus frequency. Subsequently there was a development during intermittent retinal illumination of multiple spike discharges which were of greatest prominence in the occipital and parietal regions but were present in other portions of the recording area as well. Bursts and runs of higher relative amplitude slow activity in the ca. 6 per second frequency range occurred during trains of intermittent retinal illumination with considerable persistence after cessation of the stimulus. Multiple spikes of excessive relative amplitude, initially conforming to the stimulus frequency but thereafter becoming independent of it, were seen with intermittent retinal illumination at various frequencies. The interpretation was that of an abnormal electroencephalogram because of bilateral, symmetric, paroxysmal excessive evoked cerebral electrical abnormalities during intermittent retinal illumination.

Electroencephalographic findings. C. M., *Case* III 4: There was in the resting tracing a dominant, symmetric, regular ca. 9 per second alpha activity in occipital and parietal distribution. There was in the frontal and central regions and to a lesser degree in the temporal regions symmetrically, bilaterally a very high relative amplitude discrete wave form remarkably regular, ca. 30 per second fast activity. There occurred during hyperventilation some slow activity which was inconstantly lateralized. This took the form of spike and slow wave activity. During the initial period of intermittent retinal illumination there was no significant change. During the latter portion of retinal illumination there appeared bursts of slow activity mixed with faster frequencies and multiple spikes asymmetrically (left occipital and parietal). At times, if intermittent retinal illumination was continued, particularly in interrupted trains of stimuli, the slow activity of occipital and parietal regions with its intermittent spike discharge was repeated. The interpretation was that of an abnormally evoked response during intermittent retinal illumination. In the resting tracing there was fast activity of discrete wave form and high amplitude which, although symmetric, was abnormal.

Electroencephalographic findings. G. M., (mother of case III 1): This record of the mother of D. M. (case III 1) showed no abnormality in the resting tracing during hyperventilation or during intermittent retinal illumination.

Abnormalities of the type which have been described occurred in 85 of the 615 individuals in whom intermittent retinal illumination with cerebral electrical recording was carried out. In the majority of the individuals who exhibited a light sensitivity according to these criteria, there was a history of intermittent clinical disorder consistent with an epileptic disturbance or a family history of seizures. Four instances which will be discussed further below were exceptions. Four pairs of identical twins with seizures were examined.

COMMENT

The patients we have described represent a group of individuals subject to seizures which take various forms, among them, generalized convulsive seizures, "absences," and symmetric myoclonic jerks affecting limbs and axial musculature. In none of the affected individuals or their relatives was there evidence of a focal lesion of the central nervous

system. The electroencephalographic abnormalities which occurred in the resting records and during intermittent retinal illumination present certain similarities but no specific characteristics which set this group of patients apart. However, these individuals present a similarity in the general pattern of their disorder and sensitivity to light which serves to set them apart from other epileptics. We would emphasize the significance of the concurrence of seizures, myoclonus, and light sensitivity in a family setting.

It is assumed that epilepsy is not a disease *sui generis* but a symptom of an altered state of excitability of the central nervous system. In the case of symptomatic seizures of focal origin the excessive nerve cell discharge begins locally. There remain, however, a relatively large number of individuals with seizures, in whom there is no evidence of exclusive focal involvement of nervous tissue on history, neurologic, or laboratory examination. In the sense that the cause of these disorders remains hidden, they may well be termed "cryptogenic." Within this mixed group, however, there undoubtedly are a variety of classes of neurologic disorder which have seizures as a symptom among others.

In the control series there did not appear the evoked cortical occipital and parietal electrical changes of excessive amplitude and deviant morphology which were observed in the records of affected individuals of the present series. In this sense the evoked changes in the latter group were considered "abnormal." Light sensitivity of the type described occurred in none of the persons in the control series in which there was clinical or electroencephalographic evidence of exclusively focal disease. In two cases with uremic encephalopathy, one with aqueductal stenosis and internal hydrocephalus, and one with the syndrome of *dyssynergia cerebellaris myoclonica* of Ramsey Hunt, there was cerebral light sensitivity. These represented, in a sense, diffuse involvement of nervous tissue.

The nature of the electroencephalographic abnormality observed in the 39 individuals found to be light sensitive in this group of 16 families is one which is consistent with a diffusely distributed disorder of neuronal function. The initial site of the abnormally evoked potential is the occipital and parietal cortex bilaterally and symmetrically. In susceptible individuals persistence in stimulus results in progressive augmentation of amplitude and areal spread of the abnormally evoked discharge; at this point clinical symptoms and signs of myoclonus may occur (for example, J. D., case III 3, Family C). With perseverance in stimulus there occurs a transition from myoclonus to a self-sustained generalized epileptic seizure, a transition of variable rapidity of evolution depending upon the stimulus parameters. Such an evolution through myoclonus to the generalized seizure has been shown to occur with diffusely distributed neuronal disease.[18]

The gradual augmentation of amplitude of the evoked occipital and parietal response with each successive flash stimulus, not seen in the control observations, implies an abnormal degree of recruitment; the widespread areal involvement implies excessive radiation. These features taken with the bilateral and synchronous characteristics of "after discharge" and the evolving widespread independence of stimulus frequency imply a disorder of synaptic resistance. The temporal relation of the abnormally evoked cerebral response with the sym-

metric myoclonus and the precipitation of a generalized seizure in an asymptomatic individual with epileptic relatives also imply the existence of an abnormal alteration of central excitatory state characterized by diminished and unstable synaptic resistance.

It is evident that the process of which the epilepsy is a manifestation is a relatively benign one in these particular individuals, in the sense that there is neither early nor definite evidence of degenerative disease. In this regard it is of interest that Antoni[29] has pointed out the existence of a dominant genetically determined epilepsy with a good prognosis. It is reasonable, as Alström[30] emphasized, that existing dominant diseases should as a rule be benign, malignant diseases being effectively eliminated by natural selection.

There is insufficient material as yet in the present series to undertake a detailed analysis of the mode of genetic transmission. Such a study is now in progress.

Bickford, Daly, and Keith,[21] in an excellent study of the convulsive effects of light stimulation in children, have described three classes of patients with regard to sensitivity to light: 1) a clinically sensitive group in which light of the intensity encountered in daily life is capable of inducing clinical phenomena; 2) a less sensitive group in which clinical seizures can be induced only under conditions of high intensity illumination and rapid flicker; 3) a group in which the only evidence of sensitivity is the occurrence of seizure discharge in relation to stimulation by light unaccompanied by any clinical evidence of seizures. Our experience is in accord with these findings. On the basis of our present study it would appear quite reasonable that siblings, co-twins, and relatives of individuals in Bickford's groups will exhibit similar evidences of light sensitivity.

Clearly the sensitivity to light in terms of evoked electroencephalographic abnormalities has as its basis a variant of the disorder of cerebral function which is manifested by abnormalities during hyperventilation. It is notable that, of the four pairs of identical twins examined, the two pairs found to be particularly light sensitive were relatively insensitive to hyperventilation, and conversely the two pairs of twins showing excessive spike and wave discharge bilaterally and synchronously during hyperventilation were those in which light sensitivity was not evident. Certainly, however, some degree of light sensitivity and overventilation sensitivity may coexist in the same family and indeed in the same individual.

Predisposition to epilepsy implies a pre-existing condition of cerebral dysfunction which, under appropriate conditions of stimulus, results in the occurrence of seizures. Light sensitivity occurs in asymptomatic relatives of individuals subject to seizures. Such persons may experience minor or major seizure phenomena for the first time while exposed to intermittent retinal illumination. Thus, it would appear reasonable to conclude that light sensitivity is one manifestation and, to an extent yet to be determined, an indication of an hereditary predisposition.

Watson and Denny-Brown[18] pointed out that myoclonus epilepsy may assume partial forms, such as self-limited seizures of childhood, and that the syndrome may follow a relatively benign and remitting course. A review of the problem of myoclonus epilepsy indicated that it

uniformly resulted from diffuse neuronal disease and that it was a distinctive feature of a series of types of degenerative encephalopathies ranging from subacute inclusion body encephalitis, through the more chronic juvenile amaurotic familial idiocy and related lipidoses, to the mildest of chronic or arrested states appearing at any age.

That the cerebral dysfunction in the present group is a manifestation of a genetically determined, diffusely distributed neuronal affection is a hypothesis with which the clinical physiologic and genetic data are in accord.

CONCLUSIONS

1. Stimulus sensitivity appearing as evoked cerebral electrical abnormalities with or without clinical seizures as a result of intermittent retinal illumination occurs as a manifestation of a genetically determined disorder of central nervous system function.

2. Clinical phenomena may take the form of generalized seizures, myoclonus, and minor alterations of awareness with onset in infancy, childhood, adolescence, or adulthood; febrile seizures or self-limiting seizures of childhood. There may or may not be knowledge of light or other stimulus sensitivity as a precipitating factor.

3. Stimulus sensitivity of the type and under the conditions described may be utilized as one means of determining the existence of a predisposing susceptibility to clinical seizures in an asymptomatic individual, with or without family history of seizures.

4. The clinical and physiologic characteristics and the genetic pattern of the disorder occurring in individuals of the 16 families described are consistent with the hypothesis that there exists a syndrome which is a manifestation of diffusely distributed neuronal disease, albeit with local emphasis.

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■ Of late, a much more rational view has been proposed concerning the relations of the cerebellum and sensibility. An eminent physiologist, Dr. Carpenter, at first suggested that this organ is probably the special seat of the so-called muscular sense to which we owe the guidance of our movements. In the last edition of his *Human Physiology*, he explains that the cerebellum may only react, by reflex action, upon the impressions that reach it, without being itself the instrument of communicating such impressions to the consciousness. Recently Mr. R. Dunn, in an interesting work, has adduced a case in proof of the view that the corpora dentata of the cerebellum are the seat of the muscular sense. In a child there was an imperfect paralysis of the right side, both of the arm and leg, but still they responded to the mandates of the will; she could move her arm about, and could grasp anything firmly enough to her right hand, when her eyes and attention were directed to it; but if they were diverted to something else, and the volitional power withdrawn, she would let the object that she had been holding fall from her hand, and without being conscious of the fact. At the autopsy, there was found in the lateral lobe of the cerebellum, on the left side, a mass of tubercular deposit a little to the outer side of the median line.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

The Ramsay Hunt Syndrome

Geniculate Herpes

Ernest Sachs, Jr., M.D. and Reginald K. House, M.D.

THE DISTINGUISHED American neurologist, James Ramsay Hunt, has been associated with several syndromes which he was the first to describe. We refer particularly to the one describing so-called geniculate herpes zoster,[1] to which he devoted greatest attention from the time of his first paper in 1906 until his last paper on the subject in 1937, the year of his death.[2] It is the extraordinary rarity of a case of geniculate herpes zoster, verified by autopsy, that prompts this report. In fact, so far as we have been able to determine, only four such cases have been reported previously.

Hunt was able to procure a post mortem on only one of his cases. This was a man aged 48 who died more than 11 weeks after an attack of herpes zoster in the occipitocervical distribution, which had caused a homolateral facial palsy. There were no vesicles within the auricle. Pathologic changes in the posterior root ganglion of the third cervical nerve as well as in the nervus intermedius (Wrisberg) were found, but unfortunately the geniculate ganglion was not examined.

Hunt classified herpes zoster at the cephalic extremity of the body according to the sensory ganglion involved, determined by the site of the rash: 1) geniculate herpes zoster (herpes oticus), 2) gasserian herpes zoster (herpes facialis), and 3) cervical herpes zoster (herpes occipitocollaris). Hunt[5] also classified the different clinical types of his syndrome as follows: 1) herpes oticus with no neurologic signs, 2) herpes oticus with facial palsy, 3) herpes oticus with facial palsy and auditory symptoms, and 4) herpes oticus with facial palsy with accompanying auditory and labyrinthine symptoms.

The so-called "zoster zone," ascribed by Hunt to the geniculate ganglion, included the tympanic membrane, external auditory canal and meatus, and the lateral surface of the auricle, concha, antitragus, and the antihelix and its fossa.

Almost 30 years later Maybaum and Druss[3] reported a case with autopsy and examination of the geniculate ganglion. Their patient, one with periarteritis nodosa, had swelling of the face and about the eye, deafness, and palsy of the right side of the face four and a half months before death. Six weeks before death, however, herpetic vesicles occurred on the left tympanic membrane and auricle,

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This work was supported by a grant from the Hitchcock Foundation, Hanover, New Hampshire.

followed by partial left facial palsy. At autopsy, examination of the left geniculate ganglion revealed cells described as "disintegrated, shrunken, and pyknotic."

Ten years later, in 1944, Denny-Brown, Adams, and Fitzgerald[4] reported a case in which there was an herpetic eruption over the back of the head and neck but not involving the auricle. On the eleventh day of his illness this man developed a homolateral peripheral type of facial palsy and the tongue deviated to the right. The patient died 64 days after the onset of the illness. Their report reads: "The paralysis was accompanied by a new eruption of vesicles over the posterior aspect of the right side of the head. Hearing was acute. There was impairment of pain and touch sensation over the second and third cervical segments on the right side, the area corresponding to that of the cutaneous eruption."

The authors mentioned that the skin in the right external auditory canal was swollen, red, and desquamating, whereas in the right occipital and postauricular regions there was a vesicular eruption as well as dry, scaly papules which represented older lesions. They also pointed out that pain was severe and limited to the right side of the face, occiput, and neck, preceding the eruption by two or three days. No vesicles were ever observed within the right auricle nor was pain within the ear mentioned.

This condition was, therefore, characteristic of cervical herpes, not herpes oticus. Autopsy showed that the second cervical ganglion was virtually destroyed. Most of the cells in the third cervical ganglion were intact. The geniculate ganglion contained a normal complement of cells, none of which appeared to have suffered any damage, nor was there any inflammatory reaction. These authors used this case to demonstrate that "the evidence for geniculate ganglionitis in the Ramsay Hunt syndrome was invalid," because of the fact that a typical second cervical ganglionitis was associated with involvement of the facial nerve without damage to the geniculate ganglion. This, however, is inconclusive. It does not prove that geniculate ganglionitis may not occur, and might not cause facial palsy in cases of herpes involving the auricle. Indeed, as Spillane[5] pointed out a decade later, "In view of the demonstration that herpetic infection of the relatively remote cervical ganglia can cause a neuritis of the facial nerve there can be no objection to the idea of geniculate infection doing likewise. But we know now that invasion and not compression of the facial nerve is the likely mechanism of involvement."

Findlay[6] reported the fourth and only other previous autopsy we have been able to find in a case of geniculate herpes. This patient was a male, age 52, who died three months after an attack of herpes zoster involving the left external auditory canal and the "cavum conchae." Complete left facial paralysis lasted until the time of his death caused by a ruptured gastric ulcer with peritonitis. Pathologic examination of the left petrous bone, the geniculate ganglion, and neighboring structures was carried out. Most of the cells of the geniculate ganglion were well preserved, but some showed degenerative changes, cytoplasmic shrinkage, nuclear pyknosis, and, in some, the nerve cells had lost their nuclei. Findlay noted lymphocytes and a few plasma cells scattered through the ganglion. In the facial nerve there was some lymphocytic cuffing around

blood vessels, but even more marked inflammatory changes were present around other blood vessels and in a nerve trunk found in the bone close to the ganglion. This was a case of true herpes oticus.

The authors present the following case, the fifth on record with autopsy.

Case 1. A 70 year old man was admitted to the hospital on August 15, 1952. Twelve days before admission he had felt weak and light headed. There was a dull headache and his right ear had become painful. He had a constant ache in the ear, with occasional twinges of sharp pain. The next day he was aware that his ear was swollen, and three days later he found that his face was paralyzed. Five discrete blisters were noted within the right auricle associated with localized pain. These dried up and crusted over. During the ten days prior to admission he thought his hearing had diminished in the right ear. There was no tinnitus, vertigo, nausea, or vomiting. There was swelling and edema of the right auricle, with some crusted areas and scaling within the canal, and a complete facial palsy on the right of the peripheral type (figure 1). There was loss of taste on the anterior two thirds of the tongue on the right. An audiogram revealed a bilateral nerve type of deafness. There was no involvement of the fifth nerve. There was hyperesthesia within the auricle of the right ear and marked unsteadiness of gait with a tendency to fall to the left whether the eyes were open or closed. There was no finger-to-nose or heel-to-shin ataxia. He was discharged after seven days in the hospital.

The patient was a diabetic under good dietary control and did not require insulin. He was seen in the clinic one month later for diabetic check-up. The Bell's palsy was still complete. There was no postherpetic neuralgia. There were no scars from the vesicles within the ear. The facial paralysis subsided after many months. He died of a coronary thrombosis 14 months after onset of the herpetic eruptions. Autopsy was obtained, and both the right geniculate ganglion and the brainstem were preserved for examination.

Case 2. A 48 year old man had herpes zoster

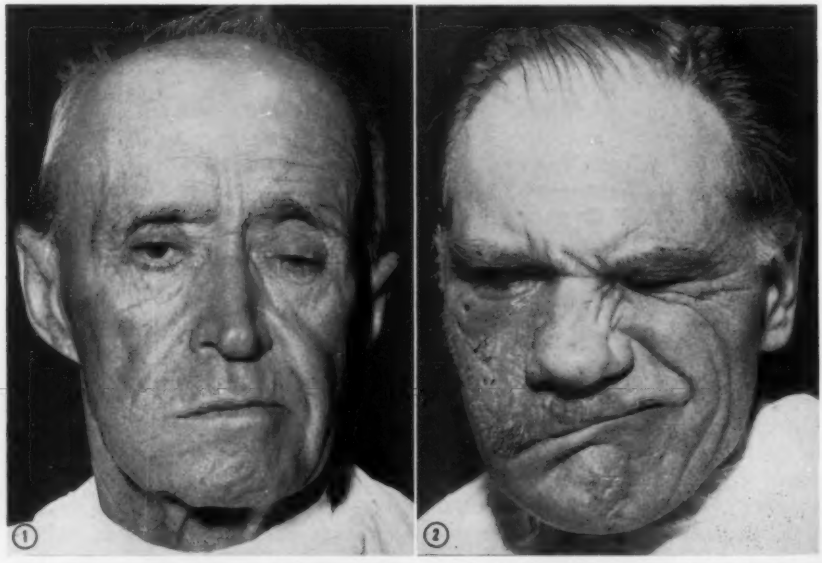


FIG. 1. *Case 1.* Patient attempting to close eyes, illustrating right facial paralysis. FIG. 2. *Case 2.* Patient trying to close eyes, illustrating incomplete right facial paralysis.

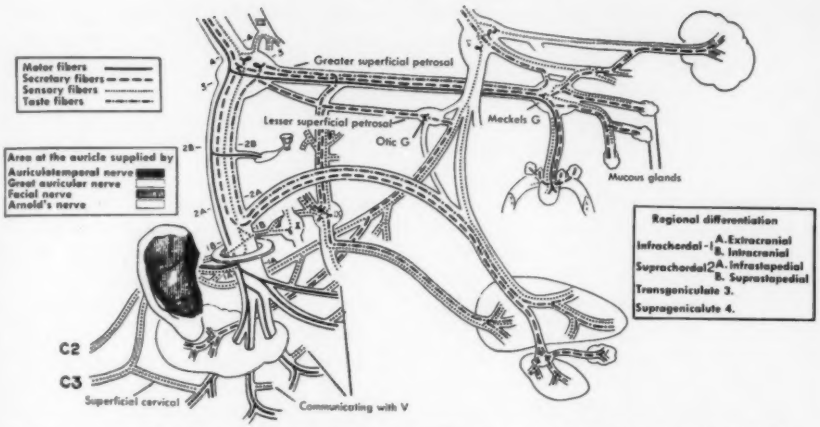


FIG. 3. Innervation of the geniculate ganglion. (Courtesy Dr. K. Tschiassny.) Reproduced from the Annals of Otology, Rhinology, and Laryngology.

of the maxillary division of the trigeminal nerve with associated facial palsy (figure 2), illustrating Hunt's gasserian herpes zoster (facialis). There was further evidence that the herpetic virus migrates, probably via the greater superficial petrosal nerve, to the geniculate ganglion (figure 3).

PATHOLOGIC EXAMINATION (Case 1)

The brain was fixed in 10 per cent formalin and sectioned two weeks later. The cerebral and cerebellar hemispheres were sectioned at 1 cm. intervals. No gross abnormalities were observed. The brainstem was removed intact. The geniculate ganglion was dissected free from the bony compartment and placed in 10 per cent formalin. Serial sections were made of the brainstem from the lower medulla to the upper pons. After every fiftieth section, three sections were saved and stained with hematoxylin and eosin, tolouidine blue, and Weigert's stain.

Histologic examination of brainstem. The pons and medulla showed little change. The meninges appeared normal. The small arteries of the brainstem showed slight intimal proliferation. One small vein in the left tegmentum had a perivascular infiltration of lymphocytes. The majority of neurons throughout all levels appeared normal. There was a moderate amount of lipofuchsin within the cytoplasm of the neurons, with some eccentricity of the nuclei and poorly stained nuclear chromatin. In the right facial nucleus there were a few neurons with changes suggesting axonal reaction. No abnormalities were observed in the abducens, spinal tract, and nucleus of the fifth nerve, pontine nuclei, vestibular nuclei, or any other structures.

Histologic examination of geniculate ganglion. Multiple sections were made of the right geniculate ganglion. These were prepared with hemotoxylin-eosin, tolouidine blue, and Bodian stains. In the sheath of the seventh nerve proximal and distal to the ganglion, there were moderate numbers of lymphocytes and plasma cells infiltrating the endoneurial and perineurial connective tissue.

In some areas the lymphocytes were in focal collections (figure 4). In one small fascicle of fibers the normal structure of the nerve appeared to have been lost. Both proximal and distal to the ganglion there were relatively few Schwann cells and no recognizable nerve fibers, either in the form of myelin sheaths or axis cylinders, with routine hematoxylin and eosin stains. In this area many fibroblasts were observed (figure 5). In the proximal part of the nerve which was probably near the internal auditory meatus, definite Schwann cells and medullated fibers were seen. Adjacent to the ganglion there were interlacing strands of connective tissue which contained apparently normal nerve fibers (figure 6). One small vein was surrounded by a lymphocytic infiltrate (figure 7). The Bodian stain revealed very few large axis cylinders in the distal segment of the seventh nerve, but there were a great number of fine ones, many of which were intertwining (figure 8). There were no end-bulbs on any of the fine fibers.

The assumption is that many of the fine fibers are regenerating axis cylinders. We can conclude that a large number of motor fibers have been destroyed and that many fine fibers have regenerated from the more proximal part of the intact fibers. This would account for the severity of the paralysis and the long delay in recovery.

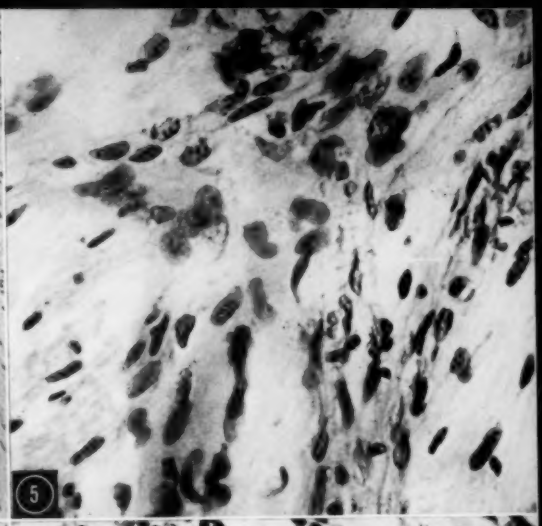
Of utmost importance, in the authors' opinion, is the fact that all sections fail to demonstrate any abnormality of the ganglion cells. Twelve geniculate ganglia, taken at routine autopsies for controls, were compared with the geniculate ganglion under discussion. Both the distribution and the number of ganglion cells were essentially the same in the present case as in the controls.

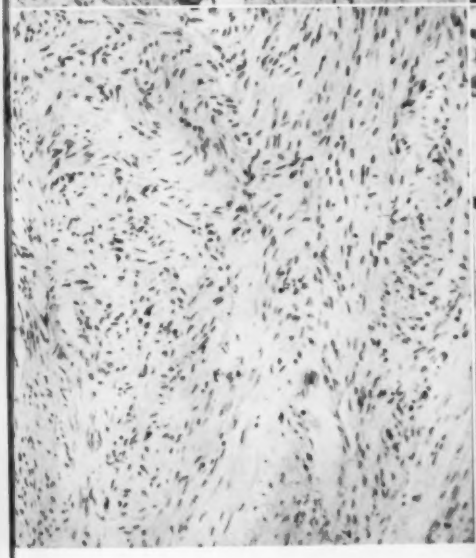
Summary of histologic findings. "There is unequivocal evidence of destruction of the seventh nerve both proximal and distal to the ganglion, but most marked in the distal segment. This is in contrast to the most proximal part of the nerve where it becomes root. Here there are many medullated fibers. Both the inflammatory reaction and the character of the lesion suggest that this has been an inflammatory process of the type produced by herpes zoster. The absence of necrosis is unusual, as is also the lack of histologic change in the facial nucleus of the pons. Many of the nerve fibers in the damaged portion of the nerve were intact but may have regenerated. The lack of inflammatory reaction in the brainstem 14 months after onset of a zoster infection is not surprising.

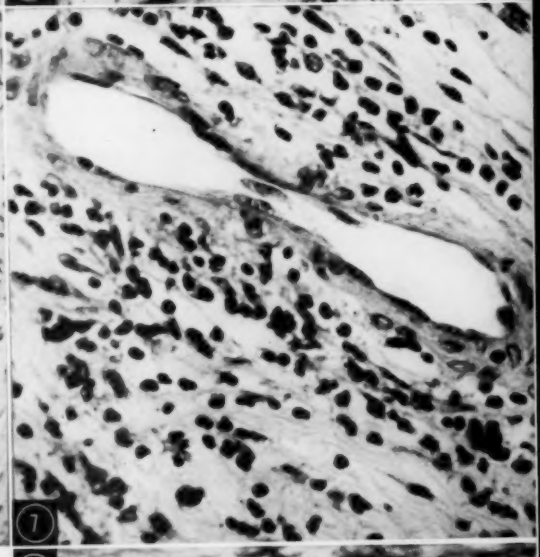
"This case does not answer several of the more difficult questions concerning herpes of the geniculate ganglion. Furthermore, we do not know whether the sensory ganglia of the ninth and tenth cranial and second and third cervical nerves were affected. The case is of interest because it indicates a fairly severe facial palsy occurring with a vesicular eruption that was limited to the external auditory canal without an extensive ganglionitis."

DISCUSSION

Throughout his publications, Hunt tried hard to establish the fact that, in addition to its motor and gustatory functions, there was somatic sensation in the facial nerve. In this respect we have little to add since our patient had no sensory loss about the ear either inside the canal or behind the pinna. We do, however, have another case in which stimulation of the facial nerve, eighth







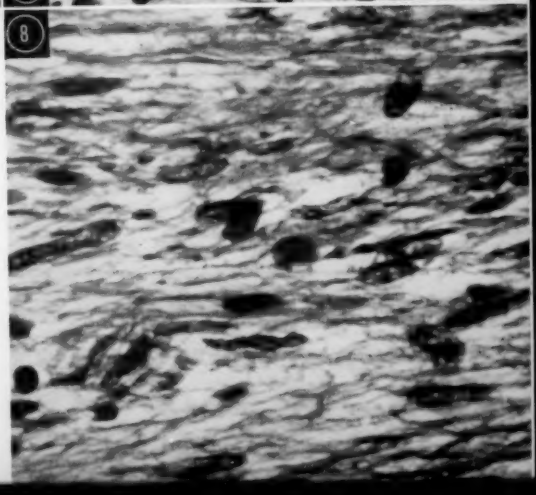


FIG. 4. Lymphocytes and plasma cells infiltrating the seventh nerve and its sheath. Hematoxylin and eosin stain.

FIG. 5. Large numbers of fibroblasts present in the seventh nerve. Hematoxylin and eosin stain.

FIG. 6. Interlacing strands of connective tissue containing nerve fibers. Hematoxylin and eosin stain.

FIG. 7. Vein in capsule of ganglion surrounded by lymphocytes. Hematoxylin and eosin stain.

FIG. 8. Fine axis cylinders in distal segment of seventh nerve. Bodian stain.

nerve, and nervus intermedius at operation under local anesthesia caused pain in the ear such as Clark and Taylor[7] and Furlow[8] described.

This case is of interest not only because it falls into the fourth, rare type with labyrinthine symptoms but also because the herpes was distinctly confined to the typical zoster zone that Hunt described. Furthermore, though pathologically there was distinct involvement of the proximal and distal portions of the seventh nerve, the geniculate ganglion itself was not involved. We feel that this emphasizes a point often overlooked regarding the pathology of herpes zoster, namely, that there is usually an encephalomyelitis and a neuritis involving both motor and sensory nerves and the lesion is not confined to the posterior root ganglion. Indeed, it is probably the central encephalomyelitis (not present in this case) which gives rise to the postherpetic neuralgia so notoriously difficult to treat. In addition, virus intracellular inclusion bodies may be demonstrated in the vesicles of the skin, suggesting that the infection may migrate along the course of the nerves, a fact which is frequently overlooked.

We are in full agreement with Spillane and Tschiassny[9,10] that Hunt overstated his thesis that herpes zoster involved the geniculate ganglion in all the above-mentioned types of the syndrome. The case presented here shows that even in this most classical form of herpes oticus with facial palsy the geniculate ganglion itself may not be involved.

SUMMARY

1. A case of herpes zoster (oticus) with facial palsy and autopsy has been presented.

2. The four previously reported cases of this syndrome are discussed.

3. Serial histologic sections showed an interstitial neuritis, both proximal and distal to the geniculate ganglion. The ganglion itself appeared normal.

4. Evidence for pain fibers in the seventh nerve is corroborated by a case stimulated at operation.

5. The widespread nature of the zoster infection is emphasized by a case involving the maxillary division of the trigeminal nerve with facial palsy.

We wish to thank Dr. Raymond D. Adams for his invaluable assistance in reviewing the histologic sections of the brainstem and geniculate ganglion, and his technicians for preparing the serial sections of the brainstem.

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Diffuse Glioma of the Brain in von Recklinghausen's Disease

A Study with Silver Carbonate

K. Scharenberg, M.D. and E. Jones, M.D.

ONLY A SMALL SERIES of observations have been made of von Recklinghausen's disease with diffuse blastomatous involvement of the central nervous system. In a review of the literature only 15 reports of this type of central pathology could be found. This presentation adds a case in which diffuse invasion of the brain occurred.

REPORT OF CASE

A 12 year old girl of average intelligence was admitted to the hospital with complaints of dizziness, difficulty in walking and maintaining balance, and tendency to fall to the left. These symptoms had been present for four months. During the four weeks prior to admission she had also had headaches with nausea and vomiting. At five years of age a "neurofibroma" had been removed from the left side of her tongue. The child's mother, who was still living, had cutaneous nodules and pigmented areas characteristic of von Recklinghausen's disease.

On examination there were numerous cafe au lait spots over the trunk and arms, bilateral papilledema of 4 diopters, enlarged blind spots, bilateral Babinski reflex, ankle clonus more marked on the right, tendency to fall to the left on walking, and dysdiadokokinesis on the left. Roentgenographic examination showed prominent digital markings over the entire cranial vault and some separation of the sutures; the sella turcica was enlarged; the clinoid processes and tuberculum sellae were osteoporotic and eroded; the lateral and third ventricles were dilated but symetric.

Exploratory craniotomy of the posterior fossa revealed partial stenosis of the aqueduct of Sylvius and a Torkelson procedure was performed. No tumor was found. The patient died two days later and autopsy was performed two and a half hours after death.

Pathologic findings. The brain weighed 1,420 gm. It was edematous and there were bilateral temporal pressure cones. There was an extensive subarachnoid hemorrhage over both hemispheres, massive extradural hematoma at the operative site, hemorrhage in the fourth ventricle around the midbrain, and small scattered hemorrhages in both cerebral hemispheres. There were no grossly visible tumors in the brain although the cerebellum, midbrain, and the base of both temporal and frontal lobes were hard in consistency.

Microscopic examination revealed a diffuse blastomatous growth in both hemispheres of the cerebellum, in the medulla, in the dorsal part of the pons, in the midbrain with partial occlusion of the aqueduct, and in the white

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Read before the American Association of Neuropathologists, June 12, 1955, Chicago, Illinois.
This work aided by a grant from the United States Department of Public Health and Welfare.

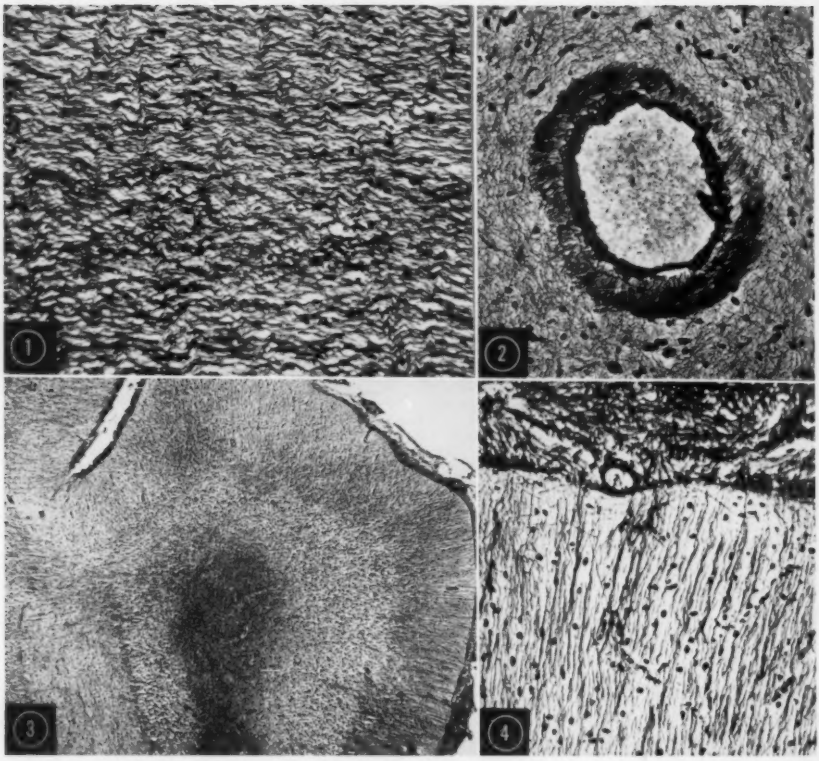


FIG. 1. Neoplastic tissue in the white matter of the cerebellum; elongated, polar tumor cells are arranged in parallel, undulating formations. Astroglia technic.

FIG. 2. Small vessel surrounded by a ring of glia fibers; blastomatous tissue is built of bi- or multipolar cells. Astroglia technic.

FIG. 3. White matter of cerebellar convolution is diffusely invaded by the neoplasm. The granular layer is greatly rarified; Purkinje cells are destroyed; molecular layer is reinforced by proliferated elements of Fananás; leptomeninges are thickened. Astroglia technic.

FIG. 4. Meninges of the cerebellum are invaded by the neoplasm and are thickened; parenchyma of the molecular layer is destroyed; elements of Fananás are proliferated. Astroglia technic.

matter of the base of both temporal and frontal lobes.

Histologic analysis showed that the pathologic tissue consisted predominantly of astrocytes, but its pattern and the types of cells varied considerably. In the cerebellar white matter the blastomatous elements were arranged in parallel, undulating formations which resembled a schwannoma; the cells had elongated nuclei and wavy, polar processes (figure 1). A dense network of fibers surrounded the blood vessels so that their walls appeared greatly thickened (figure 2). Although the white matter was extensively involved, neoplastic tissue did not invade the granular and molecular layers which were narrowed and atrophic from pressure (figure 3). The parenchyma of the cerebellum was severely damaged; Purkinje cells were reduced in number and the surviving elements were atrophic; fibers of the basket cells were mostly destroyed; in the molecular layer there was a dense network

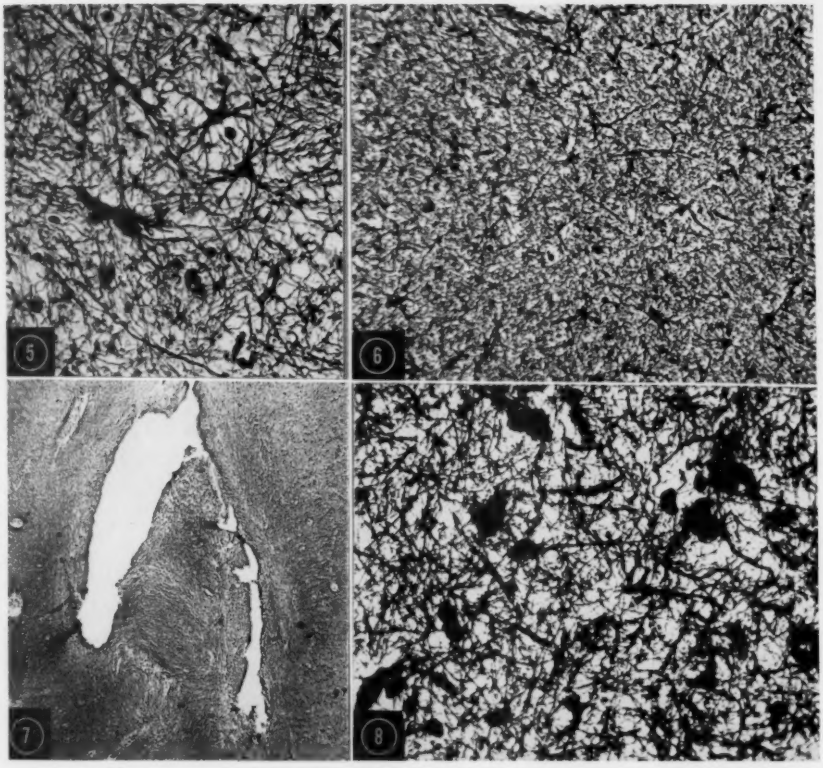


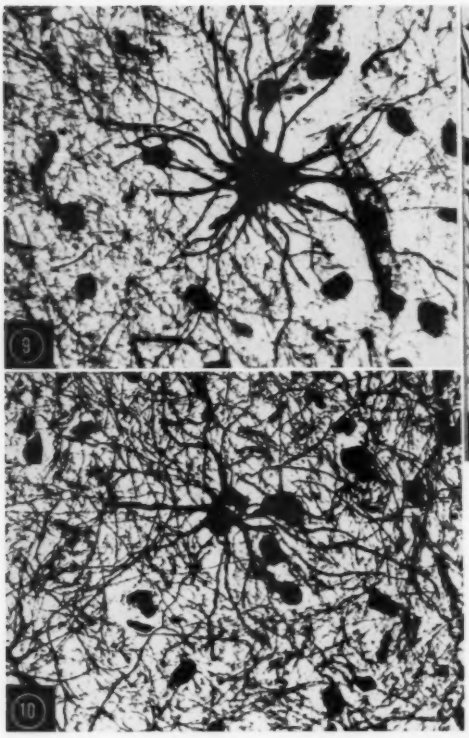
FIG. 5. Diffuse astrocytoma of the medulla built of large astrocytes which form an interlacing network. Astroglia technic.

FIG. 6. Dense interwoven network of well preserved neoplastic astrocytes in the midbrain. Astroglia technic.

FIG. 7. A tongue-like projection on the neoplastic tissue which partly occlude the aqueduct. Astroglia technic.

FIG. 8. Blastomatous tissue from the base of the right temporal lobe built of elements differentiated as astrocytes, astroblasts, and oligodendrocytes. Astroglia technic.

of proliferated and thickened fibers of the elements of Fananas (figure 4). There were a few small, scattered areas of blastomatous cells in the leptomeninges (figure 4). The neoplastic growth extended from the cerebellum into the medulla as far down as the decussation of the pyramidal tracts and up into the dorsal part of the pons and midbrain. In the medulla there was diffuse invasion by large astrocytes which formed an interlacing meshwork, but the wavy pattern which was prominent in the cerebellar white matter was not apparent (figure 5). The blastomatous tissue in the dorsal part of the pons and in the midbrain was of the same character as that in the medulla, but the astrocytes formed a much more compact, well-preserved, interwoven network (figure 6). A tongue-like projection of the pathologic tissue extended into and partially occluded the aqueduct (figure 7). The neoplasm involved the cerebral peduncles and diffusely invaded the white matter of the base of both temporal and frontal lobes, but spared the cortex and the basal ganglia. In all of these areas the growth was pre-



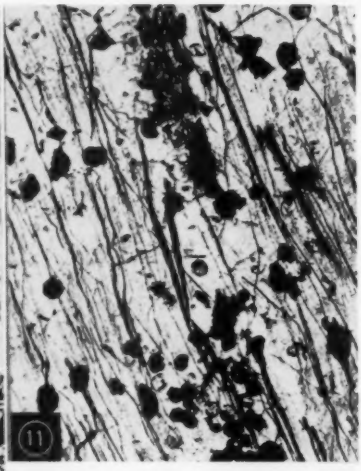


FIG. 9. Perivascular blastomatous astrocyte and numerous small elements differentiated as oligodendroglia.

FIG. 10. Large "double" astrocytes with two nuclei, interconnected cytoplasm, and long processes; numerous other cells are differentiated as oligodendroglia. Astroglia technic.

FIG. 11. Glia nodes in the molecular layer of the cerebellum built of elements with round bodies and numerous intertwined processes. This is a constant finding in von Recklinghausen's disease. Astroglia technic.

dominantly astrocytic in character, but the tumor cells varied in size and shape; some were of transitional type and resembled astroblasts and oligodendroblasts (figure 8), while others were giant, double, or triple astrocytes (figures 9 and 10). Throughout the white matter of the brain there was moderate diffuse proliferation of the astroglia.

In addition to extensive neoplastic invasion there were also scattered glial nodes which consisted of small, round, or irregular elements with numerous interconnected processes. These cells could not be classified specifically, but some of them suggested oligodendroglia. These formations occur regularly in von Recklinghausen's disease; they cause no symptoms, and in this case were independent of the diffuse neoplasm (figure 11).

DISCUSSION

The pathologic changes in the central nervous system in von Recklinghausen's disease can be classified into two main groups: extensive diffuse gliosis of the brain and discrete tumors. In both groups the above mentioned small foci of asymptomatic gliosis occur. The first group now comprises seven previously reported cases[1–7] in addition to the present one. Eight cases reported in the literature[6,8–14] fall into the second group, which will not be considered in this investigation.

All patients of the diffuse group had

evidence of von Recklinghausen's disease in other organs of the body, such as "neurinomatous proliferation" in the viscera and "neurofibromas" of the sympathetic chain[5] and of peripheral nerves,[1] tumors of the tongue,[6] and cafe au lait spots or nevi.[1,5,7] In most cases, including the one presented here, the disease was familial.

There was a diffuse invasion of various areas of the brain in all cases. In four[1–4] the basal ganglia were greatly enlarged and diffusely invaded by the tumor. Crome[7] reported "gliosis of the white matter and of the optic pathways"; Lambers and Ortiz de Zarate[6] described extensive gliomatosis of the pons, medulla, cerebellum, tuber cinereum, globus pallidus, optic nerves, and chiasma. In Walker's case[5] there was blastomatous involvement of the cerebellar folia and meninges. There is considerable similarity in the distribution of gliomatosis in Walker's case and in the one presented here, both of which showed extensive involvement of the cerebellum and midbrain; in addition, in the present case the neoplasm spread downward into the medulla and upward through the dorsal part of the pons to the base of the brain as far as the frontal and temporal lobes. Hydrocephalus was noted by Walker,[5] Lambers and Ortiz de Zarate,[6] Crome,[7] and the present authors. In Walker's case hydrocephalus resulted from overgrowth of glia in the fourth ventricle with obstruction of the foramina of Luschka and Magendie. In the authors' case the aqueduct was obstructed by a protruding glial nodule. In two cases[6,7] no cause for the hydrocephalus was stated.

Histologic findings in the present case suggested that the neoplastic tissue was variously differentiated. In the cerebellum most of the cells were blastomatous elements of Schwann, while in other areas they resembled astroblasts, astrocytes, or oligodendroblasts. This polymorphism was also noted by other authors who variously interpreted the histopathologic character of the growth. Foerster and Gagel[1] termed the changes in the basal ganglia and pons "diffuse Schwannosis." Santha[2] described oval or elongated nuclei which he considered to be lemmoblasts. Nevin[3] used the term "gliomatosis cerebri" and noted that the basal ganglia were penetrated by numerous spongioblasts and astrocytes. Benedek and Juba[4] referred to "astrocytes and uni- and bipolar spongioblasts." Crome[7] described "elongated spindle-shaped or oval nuclei and cells with indistinct margins" which he rather indefinitely termed "proliferative gliotic pan-neuropathy (gliomatosis)." Just as indefinite is the designation "central neurofibromatosis" used by Lambers and Ortiz de Zarate.[6] The picture is much clearer in Walker's case[5] which was interpreted as astrocytoma. Even though these authors arrived at their conclusions by conventional technics and thus a comparison of their findings with ours is difficult, it is apparent that the central changes in von Recklinghausen's disease may exhibit considerable morphologic variation.

SUMMARY

In the case reported here the neoplasm cannot be interpreted definitely as an astrocytoma because it also contained numerous transitional elements which resemble cells of Schwann, oligodendroblasts, and astroblasts. These findings suggest that the neoplastic cells have pluripotentiality and that the growth is related to central Schwanno-

ma, oligodendroblastoma, and astrocytoma. The neoplastic tissue was extremely well preserved, the configuration of the brain was not distorted, and edema and necrosis common in astrocytoma were absent.

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■ As regards the place of passage of the voluntary motor conductors in the medulla oblongata, I will now say only a few words. The crossing of the anterior pyramids I shall try to prove by and by to be very nearly the only one for the conductors for voluntary movements. I will merely state now that if a section is made longitudinally just at the place of the decussation of the anterior pyramids, so as to divide entirely all the decussating elements, we find that, although the animal lives some time after the operation, it has no voluntary movement at all in any of its limbs, which are almost always the seat of convulsions. A section of the two anterior pyramids is followed by the same results, while a section of the olivary columns, which are chiefly the continuation of the anterior columns of the spinal cord, does not seem to produce a notable paralysis; so that the greatest difference exists between the spinal cord and the medulla oblongata, as to the place of passage of the voluntary motor conductors.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Mescaline and LSD-25 in Activation of Temporal Lobe Epilepsy

Bert E. Schwarz, M.D., Reginald G. Bickford, M.B., M.R.C.P., Donald W. Mulder, M.D. and Howard P. Rome, M.D.

In a previous report,[1] the effects of mescaline and d-lysergic acid diethylamide (LSD-25) on 24 physician volunteers were summarized. As seen in tables 1 and 2, there is a striking resemblance between the action of the two drugs in their widespread psychic effects and to analogous phenomena which occur in the so-called functional psychoses. In general, the affective reactions and the distortion of ideational content seem to be patterned on a frame of reference colored by previous life experiences. For instance, one volunteer related much of his mescaline-induced experience in such a form as: "I have proprioceptive changes in my feet, legs, and perineum. I feel that my feet are wiggling . . . the only way to affect it is to move the muscles."

In another volunteer haptic hallucinations developed: "My face is being touched." This same volunteer experienced colored visual synesthesias of flaming crosses and waterfalls in his homolateral visual fields when figures were traced on his outstretched palm. He claimed that he was unable to perceive the touch sensation, but he envisaged it correctly. Other examples were numbness of the lower lip and auditory hallucinations of growling dogs. Another volunteer reported a feeling of contemplation and philosophic omniscience.

It was also noted that the reactions to LSD-25 were productive of uncontrollable laughing and giggling, whereas reactions to mescaline more frequently resembled the stuporous state. Two volunteers who took both mescaline and LSD-25 at different times had experiences essentially the same as those reported by Mátéfi.[2] They became withdrawn and rather catatonic after receiving mescaline, whereas they were inappropriately silly and affected by giggles when LSD-25 was used. Their drawings and autographs showed the same effects as did Mátéfi's. In no instance was there any clouding of consciousness when these drugs were used, although a subjective sense of timelessness existed for all. As an example of an intact intellect, one polylingual volunteer translated a paper on electroencephalography from Italian to French to English.

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TABLE 1

PSYCHIC DISTURBANCES IN 11 NORMAL VOLUNTEERS AFTER THE ADMINISTRATION OF MESCALINE

Disturbance	*Volunteer*										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Affect											
Anxiety (fear, apprehension)			+	+		++				+	++
Depression (somatization, facies, etc.)			+			++					+
Manic symptoms (expansive, euphoria)		++		++	+						
Withdrawal (indifference)	++				+		+	+	++	++	+++
Suspicion (facies, ideas of influence, heightened significance of objects)				+	++			++			
Sensory											
Vision (hallucinations, macropsia, micropsia, polyopia, illusions, after-images)	++	+++		+	+	++	+	+	++	++	+
Hearing (hallucinations hyperacusis)					++			++			
Body image (depersonalization, floating, unreality)	++	++	+	++	+	++	+	+++	+	++	++
Synesthesias (visual hearing, somesthetic vibrations)	+++	+++		+++	+++		+++	++	+	++	+
Motor											
Catatonia (stupor)		+		+			+	+		+	++
Thought											
Blocking (deprivation)						+	+	+	+	++	+
Loosening of associations	+	+		++	+						
Neologisms							+				
Pressure		+	+	++							

\+ = present ++ = marked +++ = very marked

In many instances the maximal effects of mescaline and LSD-25 occur after some acute stress such as exercise. One volunteer was convinced that, aside from nausea, the mescaline had no effect. However, four hours after the ingestion of 400 mg. of mescaline he took a brisk walk that precipitated his "floating back" to the laboratory, where pronounced visual hallucinations and depersonalization phenomena ensued.

The earliest visual experiences associated with the use of both drugs were similar to the visions obtained by photic stimulation alone; for instance, inanimate objects such as multicolored geometric forms were gradually recognized as Aztec art, tapestries, medieval stained-glass windows, and kaleidoscopes. Later, interpretations became more personalized, in the form of Tibetan mountain shrines, castles along the Rhine, and Nijinsky's war mask. One volunteer, who was both blue-yellow and red-green color blind, was convinced that LSD-25 had greatly relieved this defect until he was given the pseudoisochromatic plates for the testing of color perception. Other less

TABLE 2
PSYCHIC DISTURBANCES IN 13 NORMAL VOLUNTEERS AFTER THE ADMINISTRATION OF LSD-25

Disturbance	*Volunteer*												
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Affect													
Anxiety		+	+		+	++		+	++				+
Depression													
Manic symptoms (laughing, giggling)	+	++	++	++	+++	+++	+++	++	++		++	+	
Withdrawal									+	+	+		+
Suspicion				++					+				
Sensory													
Vision	+	+	+	+	++	++	+	++	+	+		+	++
Hearing										++	+		
Body image	+	+	++	+	++		++	+	++		++	+	+++
Synesthesias					++								
Motor													
Catatonia (stupor)	+	++		+			+			+		+	+
Thought													
Blocking	+	+	+						+				
Loosening of associations				+	+	++	+++	+	++			+	++
Neologisms					+								
Pressure					+								

\+ = present ++ = marked +++ = very marked

frequent visual phenomena included distortions in size, shape, and movement, such as the illusion of writhing snakes on a brick wall, micropsia, macropsia, and polyopia.

Associated with these perceptual distortions were the changes in affect. One volunteer said: "I feel indifferent; I don't care; I sit here, yet the feeling doesn't concern me; it's nirvana. I don't care to talk; but wish to be left in peace."

In one volunteer, who was outgoing and garrulous before he received mescaline, suspicious facies developed and he went into a trancelike state. He sat aware of his surroundings, yet gave no sign of recognition of his wife when she entered the room.

Another volunteer expressed his situation as, "I feel that everyone in the room is taking notes. Each glance is meant for me. They're evaluating my situation. I'm a goldfish in a bowl. All noises are intensified. I have a feeling of being different, and that my behavior might not be socially acceptable."

Another volunteer, in whom a mildly agitated depression developed, said: "I feel miserable, restless and jumpy, cold, and out of touch. It's a state of being just about to pass out, yet you stay that way."

Many of these reactions came in waves when the symptoms increased greatly, and they were commonly associated with increased nausea or vomiting or both, in addition to other autonomic changes. Rinkel[3] reported an effect of recurrent phases of dreamy confusion, with *déjà vu* and distorted bodily sensations, produced by LSD-25. Whereas mescaline seemed to cause detached reactions of suspension in the present, LSD-25 seemed to be more productive of fantasies and reveries connected with previous meaningful life experiences. Al-

though all volunteers were capable of conjuring erotic visions, all felt the action of both drugs as physically anaphrodisiac. One volunteer said he was unable to obtain an erection while under the influence of mescaline. With the exception of one volunteer, no one had any typical vestibular dreams. The one dream produced by mescaline consisted of colored three-dimensional railroad tracks winding in and out, and a microcephalic dog with pink eyes.

Hughlings Jackson's[4] classic description of the paroxysmal dream state, with the associated psychic symptoms of hallucinations, perceptual illusions, affect disturbances, forced thinking, and automatisms occurring in the presence of a relatively clear sensorium, is reminiscent of the manifold effects of LSD-25 and mescaline. Many of Jackson's classic comments, and more recently the descriptions provided by Penfield and Kristiansen[5] and Mulder,[6] are suggestive of some common substrates for both temporal lobe epilepsy and the effects of mescaline and LSD-25. For instance, Mulder mentioned the complex visual and auditory hallucinations, the strange feeling states in which the patient complains of being different or transferred back to some early memory, and the illusions of distortion of size or shape of objects. The various affect states such as terror, dread, and euphoria that are paroxysmal in temporal lobe epileptic persons all occur when mescaline and LSD-25 are employed.

Because of the gross analogy between the phenomena seen in temporal lobe epilepsy and the phenomena seen in the mescaline and LSD-25 psychoses, such as unusual memory states, various degrees of depersonalization, illusions, and the like, it seemed valid to inquire into the locus of action of these by an attempt to trigger seizures by means of drugs. This could be done by the use of certain drugs which express their effects by way of these channels in much the same way that an exploring electrode can trigger off a temporal lobe focus, producing a stereotyped, repetitive picture. Although the electroencephalographic changes occurring after the administration of mescaline and LSD-25 are minimal and difficult to interpret,[1,7,8] concomitant electroencephalographic tracings were made from three patients who had temporal lobe epilepsy. An eight-channel, Grass electroencephalograph was used, and 15 electrodes were applied in a standard manner.

REPORT OF CASES

Case 1.—A 44 year old farmer was first seen at the Mayo Clinic on August 20, 1954, with a two week history of three to ten seizures a day. He had an aura of a faraway feeling, followed by a "peculiar taste, not unpleasant, and then a smell of natural gas." On a few occasions he had a vivid hallucination of a "Japanese wrestler on television." During the seizure the patient was conscious and able to respond to questions and commands. After one minute the patient swallowed several times and took a deep breath, and the attack apparently was terminated. Occasionally he noted the sensation that his lower lip and chin were twice as large as normal, "like going to the dentist."

Results of complete physical and neurologic examinations, including the ocular fundi and visual fields, were negative. A roentgenogram of the skull revealed an intracerebral calcification in the right temporal region. The routine electroencephalogram was reported as disclosing nothing abnormal.

Activation with pentylenetetrazol (Metrazol) was carried out and, after a total dose of 250 mg. had been administered, a typical automatism developed, as previously described. It lasted one minute. Associated with this seizure was an initial, generalized discharge of four to three cycles per second that finally tended to lateralize to the right, particularly in the

sylvian area. These findings, together with the absence of aphasia, were interpreted as indicative of a lesion of the right temporal lobe. Accordingly, anticonvulsant medication was prescribed and the patient was advised to return in three months.

On December 1, 1954, the electroencephalogram showed a minimal, right sylvian frontal delta. The patient had an automatism with a "faraway" aura on hyperventilation. In an attempt to activate the hallucinatory phenomena accompanying his seizure, he was given 500 mg. of mescaline by mouth and was observed over a period of six hours. A mescaline reaction of stupor and inaccessibility developed. He had mescaline-induced visions of multicolored geometric forms and kaleidoscopic effects, but at no time did anything arise reminiscent of his aura, either directly or in the nature of a screen memory. The electroencephalogram showed only minimal and rather nonspecific changes associated with mescaline. However, the photic drive response was increased in amplitude by 50 per cent. Examination of the cerebrospinal fluid gave negative results. Ventriculography revealed shift of the lateral horns and third ventricle to the left. The patient underwent craniotomy. A brain tumor (oligodendroglioma, grade 3) was found deep in the right temporal lobe.

Case 2. A 21 year old woman came to the clinic on January 10, 1955. Birth had been precipitous and unattended, and an injury to the head had occurred at the age of three. The injury was followed by grand mal seizures, which disappeared when anticonvulsant medication was administered. At the age of eight years the patient had episodes of "blanking out," lasting approximately 30 seconds and occurring three to 30 times a day. She believed the spells were more likely to occur when she was fatigued or immediately before the menses. She said that as long as she could remember, the episodes had been ushered in with an aura of a vision. The visions have consisted of "knights in battle and beautiful gardens." Although the patient said she dreamed considerably, she maintained that the visions were very real and were different from her dreams.

Results of neurologic examination and funduscopic examination of the optic disks were normal. The electroencephalogram was interpreted as showing moderate dysrhythmia, bisylvian in location, and a focal sharp discharge in the left sylvian region. Because of the uncertainty in the differential diagnosis between temporal lobe epilepsy and petit mal seizure, activation with Metrazol was carried out. Typical attacks of petit mal with associated three per second, spike-and-wave discharges developed after the injection of a total of 350 mg. of Metrazol.

After one of the episodes the patient claimed she saw the vision of a "flower garden with the text, 'In God We Trust,' in which a fashion show was going on." It was also noted that the attacks could be triggered by flash stimulation at 15 per second.

The next day the patient received 50 gammas of LSD-25 by mouth. A reaction developed in which much inappropriate laughing and giggling were manifested and many visions were reported. In no instance was an episode of seizure induced, nor was there any electroencephalographic evidence of activation. The patient looked in a mirror and said, "My face looks too long and oval; too round; my mouth is over to the left." She said she saw "space ships, restaurants, crane hoists, waterfalls, and buildings." Much of the material was related to items in a magazine she had been looking at prior to taking LSD-25. However, she had no insight as to the significance of her associations and visions in relation to the previous experience. Throughout the period the patient looked perplexed and preoccupied. She asserted, "I'm in a dream, yet I'm not really here." Although she was a good subject for hypnosis, as determined in other studies, it was impossible hypnotically to influence any of the hallucinations produced by LSD-25.

Case 3. A 39 year old housewife came to the clinic on August 10, 1954, with a six month history of dream states with weak feelings that had occurred as frequently as once a day, just prior to her admission. The patient asserted that the attacks would last no more than a few seconds. About her dream she said, "It doesn't mean anything; it's not more than four to five sentences long. It's the very same dream over and over. It's simple. It's silly."

On one occasion the patient had a grand mal seizure, during which she bit her tongue. Results of the neurologic and funduscopic examinations were reported as normal. The electroencephalogram was interpreted as showing moderate dysrhythmia, generalized but maximal in the bitemporal areas, and suggestive of a disturbance of function of the temporal lobes.

LSD-25 in a dose of 50 gammas was given. It produced a reaction of uncontrollable crying and laughing. The patient became more pointed and direct in her speech. At times she would lapse into a trance, with fatuous facies, and giggled inappropriately to herself. However, nothing connected with the seizures was detected either clinically or electroencephalographically. Subsequently, a pneumoencephalogram and bilateral angiograms were made and were reported as essentially normal. Anticonvulsant medication was prescribed after the diagnosis of temporal lobe epilepsy had been made, and the patient was dismissed.

COMMENT

Judged on the basis of these three cases of temporal lobe epilepsy in which there were good histories of psychic aura, it would appear that mescaline and LSD-25, both powerful hallucinogenic agents, were ineffective as clinical activating agents. Hoch[9] has found mescaline capable of activating a manifest psychosis in a pseudoneurotic schizophrenic patient or in a patient with psychosis which had been relieved by prefrontal lobotomy. It would seem that the action of these drugs in producing the experimental psychosis might be a diffuse one, rather than one of selectively activating any single region, such as occurs in temporal lobe epilepsy. Although most of the thoughts of the model psychosis could be explained on experiential factors, it was surprising that virtually nothing was obtained that could be remotely linked with the auras. If the contents of the aura were conditioned by psychic factors, it would seem logical to be able to activate them or at least to produce some related associations with these drugs. Although mescaline and LSD-25 readily released other memories, visions, and the like, they could not precipitate the aura physiologically encapsulated in a damaged area and inaccessible to these drug stimuli. Although three cases are too few on which to base any conclusions, it would seem that the unraveling of the aura is more complex than has hitherto been believed. However, LSD-25 and mescaline might be useful in distinguishing a psychosis from a temporal epileptic syndrome. The psychosis presumably could be "activated," whereas the epilepsy would be refractive to these drugs.

SUMMARY

Mescaline and LSD-25, administered to three patients who had temporal lobe epilepsy, did not provoke psychic auras or any causally related material. The electroencephalographic changes were minimal and were associated with the action of mescaline and LSD-25, rather than as an activation of a focus.

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Protracted Unconsciousness Due to Closed Head Injury

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HIGH VELOCITY has become a part of every person's life because of the automobile, and this has resulted in an increasing incidence of injuries peculiar to high velocity vehicular accidents. Chief among these injuries are those of the head, usually of the acceleration-deceleration type. This type of injury results in profound abnormalities of the brain, with severe defect of consciousness being a paramount manifestation.

When the conscious defect is of short duration (less than a week), it has been considered to be compatible with a good functional return and is not in itself a very difficult therapeutic problem. When the duration of coma is longer, the general attitude is that of despair for any functional return and even for life. It is with this group that the management of the patient becomes a problem of major proportions.

There are few detailed reports in the literature of the course and prognostic significance of protracted defect in state of consciousness due to closed head injury. In the presentation of a series of such cases, consideration will be given to these factors. This is a problem of wide interest since these patients may come under the care of the general practitioner, general surgeon, or internist, as well as the neurologist and neurosurgeon.

CASE REPORTS

Case 1. A 31 year old woman was admitted to the hospital on March 21, 1953. Four days earlier she was driving a car at about 55 miles per hour when she crashed into the rear end of a parked truck. Since the accident she had been in coma with no response to any stimuli.

Physical examination revealed that the head and eyes were deviated to the right. The fundi were normal. The deep tendon reflexes were more active on the left than on the right, with increased resistance to passive stretch of the extremities on the right. There were bilateral Babinski signs and a right Hoffman sign. The pulse was 120 per minute.

Skull roentgenograms showed no abnormalities. There were fractures of the left first and right second ribs. A ventriculogram done on April 3 showed no abnormalities. Electroencephalogram showed one to three per second activity throughout.

Course in hospital. Soon after admission the patient began to react to painful stimuli with movements of eyes and right extremities. A tracheotomy was done on March 25 because the patient was cyanotic. On April 1 blurring of the entire margins of both optic disks was found, with edema that extended one-quarter of a disk diameter into the retina. The disks were elevated approximately one diopter with

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engorgement of the veins. The next day a ventriculogram was done which revealed no abnormalities. A portion of the posterior parietal cortex was sent for histologic examination. Following this procedure the papilledema gradually resolved.

On April 24 the patient was discharged to another hospital. Word was received from her mother that the tracheotomy tube was removed on May 31. The patient was discharged on June 4, 1953. She was fed by gavage until the middle of July. In September 1953 she was able to sit up and laughed when spoken to. The mother stated that the patient frowned if asked about something she did not want, and said "uh huh" if she wanted it. She said "bye" when people were leaving.

On February 26, 1954 word was received from the patient's mother that she was not able to speak well, but she could say "Mom," "Billy," and "Opal." She responded to questions by saying "uh huh" for yes and "ah" for no.

The right hand was held up near her shoulder constantly, but it could be pulled down. She was able to use her left arm and hand; however, there appeared to be some spasticity of the left fingers. She was able to move the lower extremities, but was reported to be slow with the right extremities. She was not able to walk. She was able to sit in a chair about half an hour.

It was reported that she could apparently see, but only close objects, and "listens" to television with enjoyment. She was able to hum tunes as well as she had prior to the accident.

Case 2. A 17 year old man was in an automobile accident on April 11, 1953. In addition to a head injury, this produced a large wound in the left posterior shoulder. At admission to another hospital immediately following the accident, he was in coma. A tracheotomy was done on admission because of cyanosis. He was transferred to this hospital on April 24.

On physical examination the patient responded to no form of stimuli. There were no spontaneous movements. The head and eyes persistently deviated to the left. Funduscopic examination showed bilateral blurring of the optic disks nasally, with a half diopter of papilledema bilaterally. Corneal reflexes were present on both sides. A sucking reflex was present. The deep tendon reflexes of the lower extremities were active and equal bilaterally, with sustained clonus at the knees and ankles. There was no response to plantar stimulation. There was a large open wound in the left posterior shoulder.

Urinalysis showed a 3+ albumin. The blood urea nitrogen was reported as 58 mg. per cent. Skull roentgenograms showed several linear fractures passing in different directions in the parietotemporal region.

Course in hospital. At the time of his initial hospitalization, the patient was in shock and bleeding profusely from the shoulder wound. He was transfused immediately. Following this the patient produced only 200 to 400 cc. of urine a day, with a rising blood urea nitrogen. Renal function became normal after two weeks.

On April 28, 1953 a ventriculogram was attempted without success. Portions of the exposed cortex were submitted for histologic examination. A pneumoencephalogram was then done by the lumbar route. The only abnormality was slit-like ventricles. One week later there was bulging at the operative sites, with purulent drainage which cleared under appropriate treatment.

The patient did well with maintenance of nutrition by gavage. Healing of decubiti of the head and sacrum was accomplished by debridement, skin grafting, and use of a Stryker frame with turning every two hours. No change was apparent in the neurologic status except that he was able to tolerate complete closure of the tracheotomy.

On September 30 he was transferred to another hospital for chronic care. The patient pursued a downward course with bouts of high fever and loss of weight. On January 3, 1954 the patient died.

Postmortem examination. The only pathologic abnormalities were found in the brain, which weighed 1,450 gm. with softenings and yellowish discolorations of the temporooccipital regions bilaterally and of the cerebellum. Inspection of the cut sections revealed widespread distribution of cystic areas in the gray and white matter, with moderately dilated ventricles. There was no involvement of the basal ganglia, brainstem, or cervical cord.

Histologic examination showed massive degeneration, with areas of complete loss of structure. Other areas showed decreased numbers of ganglion cells, normal glial elements, and

large numbers of compound granular cells and protoplasmic astrocytes.

Case 3. A 24 year old man received severe trauma to the head in an automobile accident on March 18, 1953 and went into coma. A tracheotomy was done immediately on hospitalization. He had multiple contusions and lacerations of the face and head, a fractured mandible, and large progressive hematoma of the right orbit, with fixed and pinpoint pupils. Deep coma was manifested by a lack of response to noxious stimuli. The deep tendon reflexes could not be obtained. No abnormal reflexes were present. On occasion all of the extremities were rigidly held in extension. On April 3, 1953 he was transferred to this hospital.

On physical examination there was response to only painful stimuli, with slight movements of the upper extremities and grimacing of the left face. The deep tendon reflexes were 2+ on the right and 3+ on the left. There were no abnormal reflexes.

Routine urinalysis and hemogram were essentially normal. Skull roentgenograms revealed no abnormalities. A lumbar pneumoencephalogram revealed dilated ventricles and increased subarachnoid marking without shift or distortion of the ventricular system.

Course in hospital. The tracheotomy was closed without difficulty early in April. The patient became more responsive by April 23, and for the first time he showed a slight response to the spoken word and made occasional attempts to vocalize. By the time of his discharge to a hospital for chronic care on June 20, he was able to sit up but could not stand. He could not obey any command or say anything more than monosyllables. There was slight relative weakness of the left upper extremity. The deep tendon reflexes were active, with the right side slightly predominant.

While hospitalized for chronic care over the next three months, he became aware of persons and locations, although he was still disoriented as to time at the end of this period. Since admission he has at times been completely incontinent of bowel and bladder, although at other times he would use the toilet and urinal if it were convenient for him. He had occasional aggressive tendencies at which time he would try to strike an attendant. During all of his hospitalization he had a voracious appetite, eating all of his own food and making efforts to obtain other patients' food. On one occasion he swallowed the contents of a bottle of hair tonic. During the day he frequently requested food. On occasion he was able to verbalize well and would make such requests as, "Please button my shirt before you go," or, "When am I going to get well?"

The relative weakness of his left side persisted, with a foot drop on the left and a Babinski sign on the right. Motor coordination was fairly good, except that he was unable to perform fine motor functions such as buttoning his shirt.

Psychiatric evaluation at this time revealed that he was disorderly in his personal hygiene and unable to stand or walk without assistance. However, he was able to propel himself quite adequately in a wheelchair. The stream of speech was slow, but the patient was able to express himself adequately for his purposes. Mood and affect appeared to be normal and appropriate to the circumstances. The patient appeared to be considerably deteriorated mentally, judging from the content of his speech, and preoccupied with the very basic needs of food, clothing, and general physical comforts. He did not express anything suggesting delusions, hallucinations, ideas of reference, or suicidal attempts. He had very little insight into his problem and was quite content as long as basic requests were satisfied, but became quite willful and occasionally aggressive when they were not.

Case 4. A 22 year old man rode a motorcycle into the side of a truck at 40 miles per hour, on December 12, 1952. On hospital admission he did not react to any stimuli. There were extensive contusions of the right hemicrania, absent corneal reflexes, fracture of the right clavicle and humerus, with a tremendous hematoma of the supraclavicular fossa on the right, and a pale and cold right hand.

On the day following admission, opisthotonos and hyperventilation with occasional periods of Cheyne-Stokes breathing were evident. Lumbar puncture at that time showed bloody fluid with normal pressure.

Because of continued respiratory difficulties, especially the problem of keeping the tracheobronchial tree free from secretions, a tracheotomy was done on December 16. Good nutritional state was maintained by means of gavage.

The patient showed progressive improve-

ment, and by January 2, 1953 he began to speak recognizable words and move his lower extremities spontaneously. The following day he was able to take fluids by mouth and tolerated complete blockade of his tracheotomy tube. On January 4 it was noted that he was making requests. He was still incontinent of urine and was shouting incoherently on January 15. A week later he was able to be up in a wheelchair and was started on a soft diet. By February 2 he was walking.

Upon regaining consciousness, it became apparent that he had complete absence of function of the fourth through eighth cervical roots and the first thoracic on the right, and a right Horner's syndrome.

He was transferred to this hospital on December 12, 1952. Physical examination showed defects in calculation, memory, and judgment, with considerable emotional lability and a tendency to confabulate. There were scissors gait and decreased deep tendon reflexes bilaterally, the defect being greater on the right than on the left, with pallor of the optic disk on the right. A right Horner's syndrome was present. The defects in nerve roots noted above were present, with some decrease in perception over the skin supplied by the right third cervical root.

A retrograde right axillary arteriogram showed a complete block of this artery just distal to the fracture of the clavicle. A cervical myelogram showed no block to the flow of Pantopaque and pseudomeningoceles at the portion of the dural sac at the region of the exit of the eighth cervical and first thoracic roots on the right.

Course in hospital. The patient's condition did not change while in this hospital. The psychiatric service felt that the patient had adequate intelligence, judgment, and reasoning to realize the consequences of his statements. Psychometric examination showed that his present functioning was low-normal, with evidence of a previous high-normal intelligence. There was evidence of severe psychiatric disturbance, which tended to decrease his ability to function effectively. Clinical evaluation of the content of speech and action would put him at an early adolescent level.

Case 5. A 22 year old man received trauma to his head and right thigh in a headon collision on January 9, 1954. On initial hospitalization he was in coma, with repeated brief spasms of decerebrate rigidity. The right corneal reflex was present and the left absent. The pupils were contracted and equal. No mention was made of the pupillary reflexes. The deep tendon reflexes were brisk and equal, with the superficial abdominal reflexes absent. There were bilateral Babinski signs. There was a puncture wound of the right thigh. At this time a lumbar puncture was done which revealed grossly bloody fluid with a pressure of 320 mm. of water.

On the day following admission it was noted that the patient first began to respond to pain. On January 11, a tracheotomy was done because of increasing difficulty in keeping the tracheobronchial tree free of secretions and mounting temperature. Immediately following this procedure, bilateral parietal and temporal burr holes were done which showed a subdural hematoma on the left, 2 mm. thick, and a thinner hematoma on the right.

On January 26 a ventriculogram showed no significant ventricular shift, with slight dilation of the right lateral and third ventricles. There was a filling defect in the right lateral ventricle, which was thought to be an organizing blood clot. Two days following the air study he was slightly more responsive and opened his eyes periodically. It was at this time that the patient was transferred to this hospital.

On physical examination the patient did not respond to auditory or visual stimuli. The fundi were normal. The corneal reflexes were normal and there was a left lower facial weakness. The upper extremities were held rigidly at his sides and extended. The right lower extremity moved only on stimulation. There was a right Babinski sign and absent deep tendon reflexes. Rotation of the head to either side increased the resistance to passive stretch of the upper extremity extensors of that side.

Roentgenograms of the skull were normal.

An electroencephalogram on January 17 showed complete absence of alpha activity and constant gross slowing, varying from ½ to 3 per second. The activity tended to be somewhat slower on the right, particularly in the posterior quadrants. No spike or other seizure activity was evident. A repeat electroencephalogram on March 20 showed 5 to 7 per second waves.

Course in hospital. About February 21 the upper extremities became flexed at the elbows, and he began moving his left upper extremity

spontaneously. On February 28 he still did not respond to auditory stimuli; however, he closed his eyes if approached from the left by hand or light. Painful stimulation produced an expression of pain and caused further flexion of his left forearm.

The forearms were flexed on the arms and the lower extremities were extended and spastic, with the feet inverted as well as extended. Examination of the reflexes showed no abnormal signs except for a left Babinski sign. The deep tendon reflexes of the extremities were normal except for a predominance of the right biceps reflex over the one on the left. On March 2 noxious stimuli produced slight movements of the right hand and forearm.

TABLE 1

SUMMARY OF CLOSED HEAD INJURIES WITH PROTRACTED UNCONSCIOUSNESS

Case	*Length of Unconsciousness*	*Termination*
1	3½ mo.	Recovery
2	9 "	Death
3	4½ "	Recovery
4	3 wk.	Recovery
5	4 mo.	State continues
6*	25 days	Recovery
7*	17 "	Recovery
8*	3 mo.	State continues

*Cases from Echols' series.

DISCUSSION

In this paper the common features of the clinical picture and course of head injuries have been presented, with evidence that effective treatment can salvage many of these patients. The only presentation of similar cases in the literature was mention of three cases by Echols and his associates[1] in a discussion of the use of tracheotomy in coma. One of these cases had a period of unconsciousness of approximately 25 days and was ambulatory on discharge. The second was found to be able to walk well, except for a mild aphasia and right hemiparesis four months after being unconscious for 17 days. The third was still unresponsive at the end of a 90 day period.

The paramount feature of the cases under discussion is prolonged unconsciousness due to closed head injury. This state was reversible in three out of the five cases presented; in two of these there was improvement to the point of ambulation and speaking, although in one of the cases there was considerable residual mental defect. There is a possibility that a longer follow-up would reveal further improvement, but unfortunately contact was lost with the patient. With Echols' series, a total of five cases out of eight showed recovery from unconsciousness and three of these showed considerable improvement.

It is notable that only one of the cases presented in this paper had a fracture of the skull which was minimal and linear without distortion of the shape of the calvarium. This is striking clinical confirmation of the thesis of acceleration-deceleration brain injury advanced by Denny-Brown and Russell.[2] Certainly there is very little distortion of the skull and compression of the contents when there is so little change in the skull.

The residua were intellectual deficit, aphasia, and pyramidal system defects, with one case of cervical spinal nerve root avulsion. There were no signs of brainstem pathology. This, plus the general clinical picture as described by Cairns,[3] would indicate that the injury did not affect the pons or medulla and that the site of the lesion producing the consciousness defect was probably in the region of the third ventricle and aqueduct.

Microscopic examination of the biopsies taken 12 days after accident in the first case and 17 days after injury in the second case showed the changes de-

scribed by Schienker[4] in closed head injuries. There was marked edema manifested by a spongy appearance of the tissue, with distention of the perivascular and pericellular spaces associated with venous and capillary stasis. The marked edema seen under the microscope was confirmed by the air study which showed the ventricles to be mere slits in the second case.

Electroencephalographic studies were made on the first and last cases. The study on case 1 was done two weeks after the accident, and showed 1 to 3 waves per second of moderate amplitude with some flattening in the right parietal region. The study in the last case was done a week after the accident, and this showed a complete absence of alpha activity with the waves being ½ to 3 per second. Three months later another tracing was made, which showed marked improvement with 5 to 7 waves per second throughout the record. These findings parallel those that have been previously described in closed head injury.[5–7]

Development of an effective mode of treatment has led to more frequent cases of prolonged unconsciousness. Prior to this therapy, a patient in coma either recovered quickly or died. The most important single therapeutic procedure is the tracheotomy, without which it is impossible to maintain an unconscious patient more than a few days without serious respiratory complications. Bedside suction is insufficient to keep the bronchial tree clear of secretions, even with an endotracheal tube in position, and suction also produces severe traumatic swelling of the upper respiratory tract. These abnormalities produce anoxia and initiate the vicious cycle of depression of the respiratory center, followed by decreased respiratory movement, which leads to more anoxia and pooling of secretions.[8–9]

Frequent turning is necessary to prevent the development of decubiti and helps in the prevention of pneumonia. Nutrition and fluid replacement are easily maintained by means of gavage with supplemental vitamins in the feedings. Previously an indwelling Foley catheter with a simple bedside bottle was used, but patients were plagued by frequent severe urinary infections despite the use of prophylactic chemotherapy. Tidal drainage as described by Munro[10] has proved a more effective measure.

Physiotherapy with daily passive movement of all joints through a full range of movement has been found to be important in preventing ankylosis and shortening of muscles and tendons, and is especially important for spasticity. In these patients plaster splints may be used between exercises to aid in the prevention of contractures without the development of pressure ulcers.

CONCLUSIONS

Five cases of closed head injury have been presented which showed many features in common. In each case there was a "blunt" blow of considerable magnitude to the head due to a motor vehicle accident, with little damage to the calvarium and its coverings. This produced a prolonged defect in consciousness. The patients who recovered showed no defects that could be ascribed to a lesion of the brainstem, despite many signs of considerable supratentorial pathology. These patients responded well to a therapeutic program of early tracheotomy, frequent turning, gavage, tidal drainage, and early physiotherapy.

Electroencephalographic studies were similar to those previously described in head injury and coma, but the abnormalities were present longer than usual. The histopathology was the same as had been previously represented in the literature, with the exception of more prolonged presence of edema. The findings in these cases indicate that the consciousness defect was due to a lesion in the region of the posterior portion of the third ventricle or aqueduct.

Recovery appears to be a function of the duration of disturbance of consciousness, with less than a month being compatible with fair to good brain function. Patients with a marked defective conscious state from one to three and a half months had a very slow recovery of function, and it was not possible to tell what will be the ultimate result. Those whose loss of consciousness lasted longer than three and a half months showed no degree of recovery.

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■ In cases of alteration occupying a great length of the posterior columns, there is a notable diminution in the power of standing and of walking, and when the affection has lasted long, there may be a complete loss of these powers. The causes of this weakness are: 1st. That the posterior columns, as we shall show hereafter, are the principal channels for the excitations which produce reflex movements, so that when they are altered there is a great diminution of these movements, and as they are absolutely necessary for the actions of standing up or walking, it seems very plain that these actions become lessened when the posterior columns are altered. 2nd. That after a time, when an alteration exists in these columns, the amount of power of action in the other parts of the spinal cord diminish.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Investigation of the Primate Amygdala: Movements of the Face and Jaws

2. Effect of Selective Cortical Ablation

Maitland Baldwin, M.D., Laurence L. Frost, Ph.D. and Charles D. Wood, M.S.

IN THE SURGICAL TREATMENT of temporal lobe seizures we routinely explore the mesial temporal region with a gentle electrical current. Quite frequently this stimulation is followed by movements of the ipsilateral face and the jaws. These motor responses occur when the tip of the electrode is in or very near to the amygdaloid nucleus. These movements are not accompanied by any of the characteristics of epileptiform activity, and the patient is conscious and aware of them at the time of stimulation.

In the experimental laboratory we have evoked movements of the face and jaws during electrical stimulation of the amygdaloid nucleus of Macaca mulatta. These responses which occur in the ipsilateral face and in the jaws of this monkey seem analogous to those observed during electrical stimulation of the mesial temporal region in human beings.

We have reported these observations as they were made in the operating room and the experimental laboratory in a previous communication.[1]

In a further consideration of the nature and origin of these facial and masticatory phenomena it seems appropriate to consider the motor cortex as it lies close to the upper bank of the sylvian fissure. Obviously there is a functional representation for face, lips, jaws, and tongue in this area of excitable cortex.

Furthermore, since Schneider and Crosby[2] have shown that movements of face (as well as other movements) can follow stimulation of the temporal cortex, we must find out if this large area of gray mantle is essential for the production of the movements which follow amygdala stimulation.

As a first step in this inquiry we have ablated the motor and/or the temporal cortex in experimental animals. We excised this cortex in order to find out if we could obtain movements of the face and jaws from electrical stimulation of the amygdala after excision.

MATERIAL, METHODS, AND TECHNIC

The experimental animal was the Macaca mulatta. In each animal bipolar electrodes of stainless steel were directed toward the amygdala with the stereotaxic apparatus. These electrodes were

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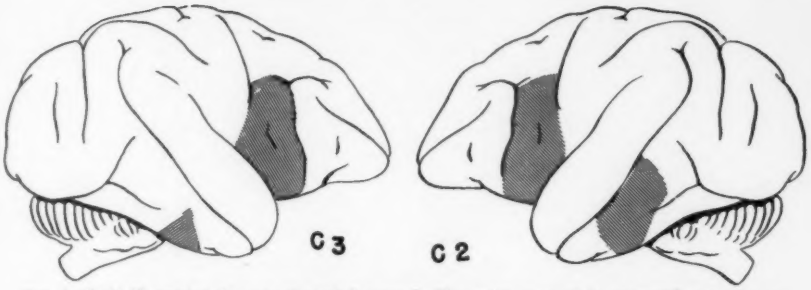

FIG. 1. *(Left)* Illustrating the area of cortical removal. The cortex removed in precentral area gave responses in the form of movements of face, lips, jaws, and tongue. From the small area of temporal cortex which was removed, we obtained movements of face, lips, and jaws.
FIG. 2. *(Right)* The cortex removed in precentral area gave responses in the form of movements of face, lips, jaws, and tongue. From the area of temporal cortex removed, we obtained positive responses in the form of movements of face, lips, jaws, and contralateral upper extremity.

secured to the skull with an acrylic substance. We have previously described the details of this technic,[1] as have Bradley and Elkes.[3] In each animal the amygdala was stimulated separately. In this fashion we obtained movements of the face and jaws.

The cortical representations for face, lips, jaws, and tongue were removed in six chronic and two acute preparations after establishing this functional representation by electrical stimulation of the cortical surface. In two chronic and two acute preparations areas of the lateral temporal cortex were removed on one or the other side. We had obtained movements of the face from these areas.

The cortex was removed in a precise manner using a subpial suction dissection technic.[4,5]

The anesthesia was pentobarbital (0.5 cc./kg. body weight). All chronic preparations made good recoveries from operation and all were permitted a reasonable period of postoperative recovery before further examination.

OBSERVATIONS

In six chronic and two acute preparations we outlined the motor representation for face, lips, jaws, and tongue by electrical stimulation, and removed this cortex.

In two chronic and two acute preparations electrical stimulation of the temporal cortex has been followed by movements of the face and jaws. This stimulation was carried out at 1.5 to 3 volts, 40 cycles, 2.5 millisecond duration. Once movements had been obtained from the temporal cortex, we removed the area which seemed related to these movements. In at least one of these cases we were able to evoke the same movements from the underlying white matter for a short time after the cortical removal. We were careful lest the stimulus spread to the underlying dura or to distant structures elsewhere. There was no evidence to suggest such spread. Actually we have stimulated the dura close to the internal auditory meatus after removal of the brain. Ipsilateral facial movements appeared with a parameter of only 0.7 volts. This observation indicated the need for care in the prevention of spread of stimulus during either cortical or deep electrical exploration.

We have removed motor cortex for face, lips, jaws, and tongue, as well as

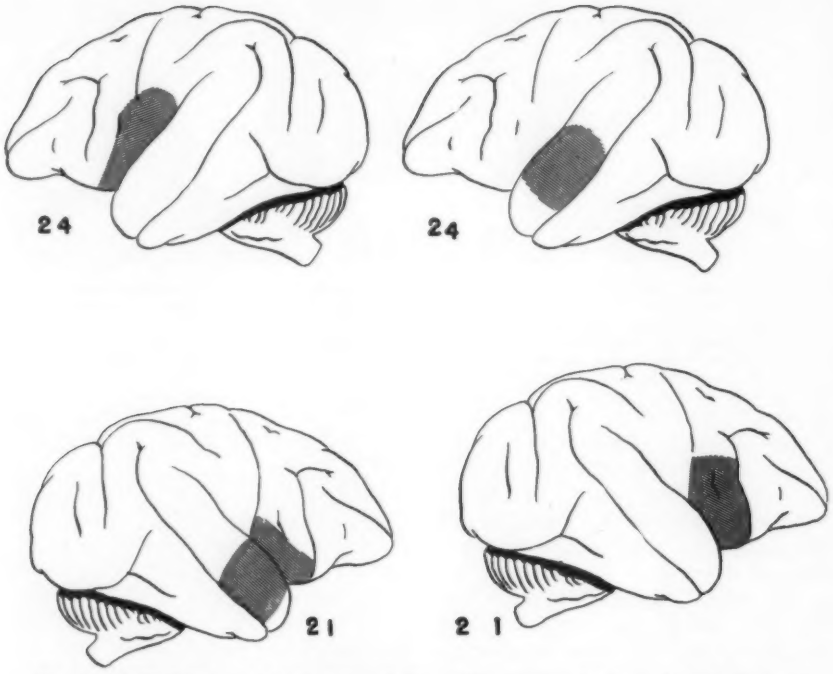

FIG. 3. This illustrates areas of cortex removed after positive responses had been obtained. These responses were in the form of movements of face and jaws. In some cases stimulation of the temporal cortex also evoked movements of the contralateral upper extremity.

segments of the lateral temporal cortex on both sides in several cases. In illustration we may present the brain diagram shown in figure 1. This illustrates removals of cortex in the right cerebral hemisphere. Figure 2 illustrates cortical removals from the left cerebral hemisphere. The remaining cortical removals are illustrated in figures 3 and 4.

We excised the precentral cortex for face, lips, jaws, and tongue in both chronic and acute preparations. Likewise, we have removed areas of lateral temporal cortex on both sides in chronic and acute preparations. In all these cases we have obtained movements of face and jaws after stimulation of one or the other amygdala.

There were other movements in the face besides those of lips and jaws. These movements also followed stimulation in the substance of the amygdaloid nucleus. The most common of these was a closing of the ipsilateral eye. This occurred slowly and was almost a sly wink. Occasionally the ipsilateral cheek seemed to wrinkle and pucker and almost reach the ear. This always followed eversion of the ipsilateral upper lip when the stimulus initiating that movement was long continued or repeated as numerous single shocks. There were occasional

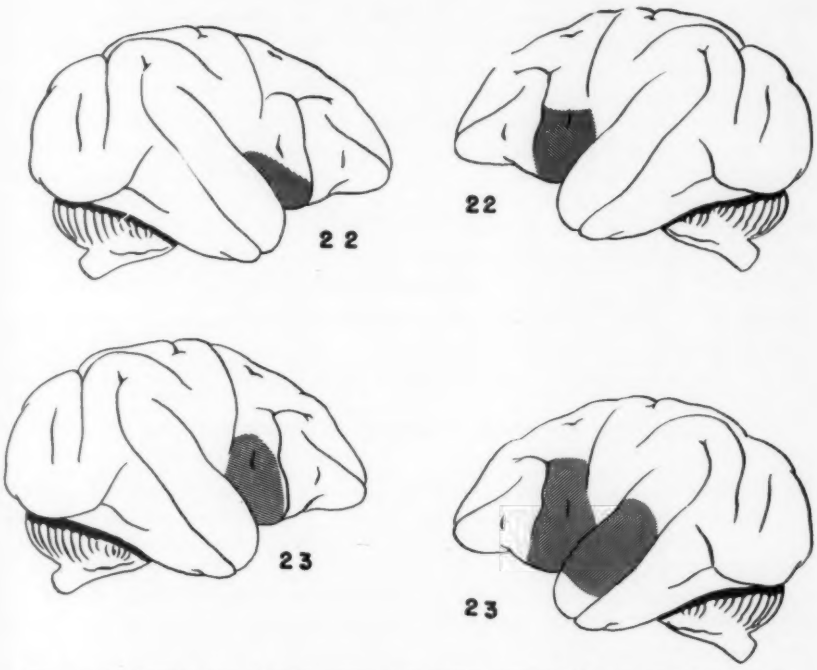

FIG. 4. This illustrates areas of cortex removed after positive responses had been obtained. These responses were in the form of movements of face and jaws. In some cases stimulation of the temporal cortex also evoked movements of the contralateral upper extremity.

movements of tongue, but these were difficult to observe and, in the conscious animals, difficult to assess. The forehead wrinkled bilaterally in some animals following ipsilateral stimulation. When the movements became bilateral, the contralateral eye often closed or opened if already closed, and the contralateral cheek puckered as well. The most common jaw movement was clenching. This was particularly true in the anesthetized animals, but we have also noted some chewing as well as an opening and forward thrust of the jaws in anesthetized cases. Chewing has also occurred in the unanesthetized animals.

All animals showed some autonomic responses. The most common of these was a change in respiration. This was an inspiratory arrest which began promptly with stimulation and ceased abruptly as the current was turned off. We used an electrocardiographic tracing in six cases. Tachycardia was observed in only one animal. Salivation occurred occasionally and was profuse and watery.

Single-shock stimuli in conscious animals were followed by a panoply of movements. The most common of these remains eversion of the ipsilateral upper lip. Occasionally the animal seemed to open his mouth and sometimes he closed

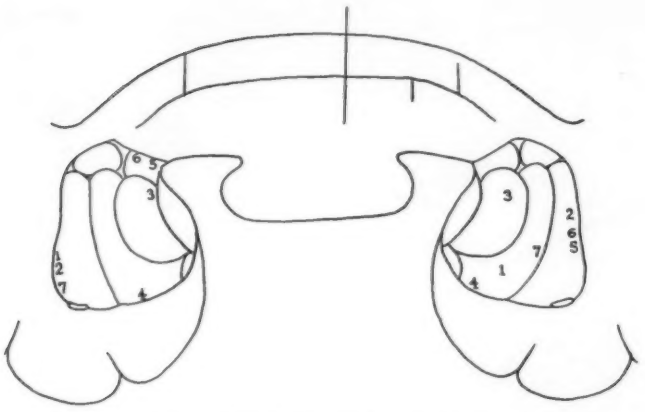

FIG. 5. The numbers illustrate the electrode tip positions in the various cases.

the ipsilateral eye.

In the intervals between test periods we have not observed any behavior which we consider unusual. We have studied 15 chronic preparations during these intervals. All of these animals had small lesions in one or the other amygdaloid nucleus. Three of them had lesions in the anterior commissure as well. We did not notice any alterations in response to feeding, cage handling, sexual activity, or preparation handling. There was no unusual oral activity.

We have summarized the histologic evidence in figure 5. From this summary we observe that, in the present series of experimental animals, the majority of the lesions caused by electrode placement in the amygdala are somewhat more lateral and inferior than those which we have noted in a previous report. In this previous report the histologic lesions seemed to concentrate in the mesial amygdala.

DISCUSSION

These observations suggest that there are functional representations within the substance of the amygdaloid nucleus which are primarily concerned with movements of the face and jaws. The majority of movements which follow stimulation of these nuclear groups are concerned with oral activities. In this respect our observations coincide with those of MacLean.[6] We have obtained other movements as well, and it is interesting that these are concerned with turning of the head and neck and with posturing of the upper extremities. At present we cannot explain the wide distribution of stimulation points in the amygdala from which movements of the face and jaws may be obtained.

These movements have been evoked on both sides following stimulation of the anterior commissure at various points in its course. This finding suggests, in turn, that the anterior commissure bears a direct functional relationship to the substance of each amgydala and that it is related specifically with regard to the functions of mouth and jaw movement. Schaltenbrand and Cobb[7] have stimulated this pathway and obtained

licking and chewing as well as whisker movements in the cat.

SUMMARY

We have removed the cortical representations for face, lips, jaws, and tongue on both sides in different monkeys. After these cortical removals we obtained movements of face and jaws as we stimulated the amygdala on one or the other side. We have evoked ipsilateral facial movements and some movements of the jaws during stimulation of certain regions of the lateral temporal cortex. This has been the experience of Schneider and Crosby.[2] However, we removed these areas of the lateral temporal cortex. In these animals stimulation of either amygdala was followed by movements of the face and jaws identical to those which we have described in animals whose cortical areas were intact.

These studies have been accomplished with the technical assistance of Shirley Lewis, R.N. and Philip P. McGrath, B.A.

The Thalamus of the Macaca Mulatta, an atlas prepared by Dr. Jerzy Olszewski, has been used as the basic reference for stereotaxic and histologic studies.

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■ It is positively and very well known that the restiform bodies, which are the continuations of the posterior columns, pass chiefly into the cerebellum. Now, if the restiform bodies contain, as is supposed, the whole of the conductors of sensitive impressions coming from the various parts of the trunk and limbs, most of these conductors must go into the cerebellum, and only a small number pass into the pons Varolii. This is what "barred the progress" of Sir Charles Bell, and made him abandon the idea that the posterior columns of the spinal cord are the channels for sensitive impressions. Other authors have not been arrested by this difficulty, and Longet has imagined that the conductors of sensitive impressions pass through the cerebellum and go out of this organ in the processus cerebelli ad testes, under which they decussate.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Knox Finley, M.D.*

CASE PRESENTATION

DR. JAMES K. SMITH: A 53 year old white male lineman was admitted to the medical service on November 28, 1947 because of headache, weakness, and mental confusion. These symptoms had been present intermittently since an attack of "encephalitis" in 1943.

The patient was in good health until August 25, 1943 when he entered a private hospital for treatment of an acute febrile illness accompanied by pleuritic pain in the left lower chest. Physical examination was reported to be essentially negative except for "retraction of the left chest." The white blood cell count was 12,800, with 67 per cent polymorphonuclear cells and 12 per cent eosinophils. Chest roentgenogram was reported as showing a "central pneumonia." The patient's symptoms gradually subsided and he was discharged one week later.

Eleven days later he was readmitted because of a chill and elevation of temperature. A chest film showed improvement. A first strength tuberculin skin test was positive. There was rapid improvement in the patient's condition and he was again discharged to his home after four days.

Three days after returning home nausea, abdominal distress, and fever necessitated readmission to the same hospital. Shortly after this admission he began to complain of severe headache. At this time slight stiffness of the neck was noted. Spinal taps were performed for the first time in October 1943, with findings as noted in table 1. A guinea pig inoculation of the spinal fluid was reported negative for tuberculosis. Roentgenograms of the chest were now interpreted as negative. Blood counts showed slight leukocytosis with some eosinophilia (7 per cent and 10 per cent) in two of the four counts. Urinalysis was within normal limits. Negative agglutination tests were reported for typhoid, paratyphoid, brucellosis, and tularemia. The patient continued to complain of severe headache and occasional episodes of nausea, and vomiting occurred along with periodic chills and fever. After one month he was transferred to a university hospital in a nearby city. The transfer diagnosis was possible lymphocytic choriomeningitis or equine encephalomyelitis. At the university hospital where he was observed from October to November 1943, another spinal puncture was performed and the findings are recorded in table 1. The patient was discharged from this hospital after one month with his illness still active and a tentative diagnosis of equine encephalomyelitis, St. Louis type.

The patient was then reported to have developed marked mental confusion and delusions and in late November 1943 he was admitted to a VA psychiatric institution where he remained for the next 17 months. The results of several spinal punctures during this hospitalization are also listed in table 1. Without any specific therapy the patient's illness finally showed slow improvement, and in April 1945 he was discharged with the final diagnosis of psychosis with encephalitis. From the time of his discharge in April 1945 until September 1945 he enjoyed a further period of convalescence at home during which time he gradually became entirely asymptomatic, re-

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Discussed and presented at the Veterans Administration Neurology Seminar in San Francisco, California, October 13-15, 1955.

TABLE 1

SUMMARY OF SPINAL FLUID REPORTS, BASED ON FINAL HOSPITALIZATION AND AVAILABLE DATA FROM PREVIOUS HOSPITAL RECORDS

Date	Oct. 3, 1943 to Oct. 18, 1943	Oct. 21, 1943 to Nov. 30, 1943	Dec. 7, 1943	Dec. 14, 1943	May 26, 1944	June 19, 1944	July 1, 1946	Dec. 1, 1947	Dec. 18, 1947	Dec. 20, 1947	Jan. 15, 1948	Jan. 21, 1948	Feb. 3, 1948	Feb. 11, 1948	Mar. 8, 1948	Mar. 30, 1948
Color				clear	xantho-chromic	slightly xantho-chromic		clear color-less	clear color-less	xantho-chron.ic	xantho-chromic	xantho-chromic	xantho-chromic	xantho-chromic	slightly xantho-chromic	xantho-chromic
Cells	303 to 433 80%L*	100 to 200 mostly L	26	29	162 98%L	219	8	12 83%L	22 91%L	One L		6L	3L	2L	0	6L
Globulin	++		+++	++	++++	++++		++++		++++		++++	++++		++++	++++
Protein		253	210	194	600	840	150	720	1,090	1,800		1,390	950	900	380	1,300
Sugar	21.7 to 50	38		20	23				60	75				52	66	76
Chloride	770	603							750							
Colloidal gold	00000-00000	"paretic"	44555-44321	45554-43211	55555-55554	55555-55555		55555-55321		55555-55555	55555-55555	55555-55555	55555-55443		55555-54432	

*Lymphocytes.

gaining a completely normal personality and apparently perfect health. By September 1945 he felt sufficiently well to return to his work as a lineman and he was able to work for another six months. In the spring of 1946 his health again began to fail. His wife stated that he started getting dizzy spells, was upset and nervous, and had headaches. This was followed by frequent vomiting and vague abdominal distress.

These symptoms led to hospitalization at a Navy hospital on April 15, 1946 where complete investigation of the gastrointestinal tract was carried out and another spinal fluid study was obtained. After hospitalization and observation for approximately four months the patient was discharged unimproved with a diagnosis of possible atrophic gastritis.

After returning home in August 1946 he continued to complain of frequent vomiting and occipital headaches, but during the next few months he again showed slight spontaneous improvement Although he did not fully regain his health, he progressed fairly well at home until September 1947 when there was recurrence of severe headaches, weakness, and mental confusion. Early in November 1947 he experienced urinary incontinence for the first time and had one mild convulsion which was followed by transient incoordination of the right hand. Progression of the illness finally necessitated admission to this hospital on November 28, 1947 when the patient came under our observation for the first time. He was in his fifth year of illness.

The remainder of the past history was noncontributory. Venereal disease was denied by the patient and his wife, and there was no history of any familial neurologic disorders.

On admission examination he appeared to be a well developed and well nourished middle aged white man who was extremely apathetic and too weak to stand or walk without assistance. He was well oriented but confused regarding details of his illness. The temperature was 98° F., blood pressure 112/70, pulse 68, and respiratory rate 20. The heart and lungs were normal. The neurologic examination revealed unequal pupils, with the left slightly larger than the right. There was nystagmus in lateral gaze, more pronounced on looking to the right. The ophthalmoscopic examination was not remarkable and the visual fields were normal to confrontation. There appeared to be no weakness of the face or tongue and the remainder of the cranial nerves were likewise normal. There was no impairment of speech. There were no tremors but extremely poor performance on the heel-to-shin test bilaterally,

and there was some wavering and unsteadiness on attempting the finger-to-nose test. Gait could not be evaluated adequately because of generalized weakness. However, there was no difference in the strength of the two sides and no focal or segmental paresis. The deep reflexes were all very active and approximately equal. No ankle clonus could be obtained. The abdominal and cremasteric reflexes were not obtainable. There was a left Hoffmann and Babinski sign and an equivocal Babinski sign on the right. Sensory examination to the usual modalities of pain, touch, position, and vibratory sense was normal. There was no nuchal rigidity. Other physical findings were not remarkable.

The blood count and urinalysis were within normal limits. The blood Kahn was negative. The sedimentation rate was 11 mm. per hour (Westergren). The blood urea nitrogen was 12 mg. per cent. A tuberculin skin test (first test dose) was positive. The electrocardiogram was normal. The electroencephalogram showed slow medium to high voltage waves in all leads and was interpreted as an abnormal tracing indicative of diffuse cortical involvement. Roentgenograms of the chest and skull were normal. Cervical and thoracic spine films showed fairly marked hypertrophic changes but no other abnormality. Spinal puncture was performed with an initial pressure of 130 mm. of water and normal responses to bearing down and jugular compression. The findings of this and subsequent spinal fluids during his last hospitalization are given in table 1.

During the first month of hospitalization the temperature remained normal except for an occasional slight rise to a maximum of 99.6° F. He became increasingly confused and lethargic and began having generalized clonic convulsive seizures. The Hoffmann and Babinski signs became definitely positive bilaterally. There was intermittent difficulty with swallowing. In the second month his temperature occasionally rose to 102° F. In the ensuing weeks he became stuporous and finally developed decubitus ulcers and urinary infection. He died April 21, 1948.

DIFFERENTIAL DIAGNOSIS

DR. LEONARD W. JARCKO:* By the time of this man's final hospitalization he had accumulated a number of clear signs of disseminated neurologic disease. The startling findings in the cerebrospinal fluid confirmed with certainty the impression of a disorder of the central nervous system. Yet the history is not one of neurologic disease alone, and it seems wise to start with the general medical problem which the patient presented at the onset of his illness.

The history began with an acute respiratory illness characterized by fever, pleuritic pain, leukocytosis with a left shift, and roentgenographic findings of pneumonia. Cough and sputum are not mentioned and we do not know what treatment was given. In 1943 he probably received sulfonamides, possibly even penicillin. If this had been a bacterial pneumonia, the chances of complete resolution would have been good. Instead, after a brief period of apparent improvement he had a second acute episode, this time less clearly pulmonary since chest films reportedly "showed improvement." After a second apparent resolution the disease then manifested new characteristics. Central nervous system complaints appeared and the cerebrospinal fluid indicated meningeal disease. From this time until his death, although signs, symptoms, and laboratory findings fluctuated markedly, the patient scarcely regained normal health for any extended period.

This appears to be the history of an infection. The causative agent seems to have entered via the lungs, producing an acute process. Treatment failed to bring about complete sterilization and the organism became disseminated. A prolonged downhill course ensued, with evidence of predominant localization of the agent in the central nervous system and meninges.

Of the organisms which produce chronic brain and meningeal disease *M. tuberculosis* was considered. Appropriate diagnostic measures seem to have been undertaken with negative results. One early laboratory finding should probably have suggested another organism. On two occasions early in the course of this disease significant eosinophilia was noted. No chronic cause of eosinophilia, such as asthma or worm infestation, is suggested, and during the last admission the blood count was normal. In the vast majority of acute infections,

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eosinophils disappear from the circulating blood. A notable exception is coccidioidomycosis, in which moderate eosinophilia often accompanies the acute phase. Appropriate cultures of the sputum might have verified the diagnosis during the first admission. Since the patient came from an area where coccidioidomycosis has a high endemic rate, the likelihood of this diagnosis is increased. For the same reason the usefulness of a single skin test is decreased, but repeated tests combined with serologic studies might have reinforced the diagnosis. While other rarer infections and infestations could conceivably produce this picture of disseminated chronic disease, coccidioidomycosis would seem to be the most likely diagnosis.

DR. HENRY LEFFMAN:* The first problem of neurologic diagnosis is where the lesion is located. The evidence points to an initial leptomeningitis of bacterial or fungal origin in view of the clinical signs of meningeal irritation and the cerebrospinal fluid findings of pleocytosis, increased protein, and decreased sugar. From June 1944 on, evidence of active meningitis was not apparent in either clinical symptomatology or the spinal fluid. Analysis of the cerebrospinal fluid suggested a loculation syndrome beyond the foramina of Luschka and Magendi. Block of the subarachnoid space in the spinal canal was excluded by the normal dynamics. The dilated left pupil, mental changes,[1] and electroencephalogram point to the interpeduncular fossa. Here adhesive arachnoiditis can block the normal flow of cerebrospinal fluid in the cisterna ambiens. By either pressure-distortion or interference with the arterial and/or venous circulation, it can also impair the function of important diencephalic-mesencephalic structures. This mechanism is not uncommon. We have under our care a patient who, following a subarachnoid hemorrhage, developed interpeduncular arachnoiditis with cerebrospinal fluid block at the cysterna ambiens (demonstrated by pneumoencephalography), mental changes, and a typical parkinsonian syndrome. Following ventriculomastoidotomy the rigidity and tremor disappeared completely and he is now back at work. The remaining neurologic signs such as convulsions,[2] pseudobulbar palsy, and possible ataxia can be explained by the effect of the basilar arachnoiditis by an analogous mechanism on the circulation at the high pontine-mesencephalic level.

The second question to be answered is the nature of the etiologic process. Inasmuch as cultures of the cerebrospinal fluid and skin and agglutination tests did not reveal the causative organism, we must review the history for a clue. Invasion of the central nervous system was preceded by a pulmonary infection associated with eosinophilia. According to Willet and Oppenheim,[3] this syndrome occurs in the following conditions: 1) ascariasis, 2) trichinosis, 3) amebic infestation, 4) tuberculosis, 5) brucellosis, 6) pollinosis, 7) clonorchiasis, 8) coccidioidomycosis.

All of these conditions can be eliminated quickly except coccidioidomycosis. This is a common disease in certain parts of California and the southwestern United States. The fungus *Coccidioides immitis* is dust born and gains access to the body via the respiratory tract or occasionally the skin. First described by Posada and Wernicke in 1892 in a case from the Chaco, Brazil, it was first reported in the United States in 1894 by Rixford. It became better known in 1939 when Gifford and Dixon established the identity of "valley fever" and "desert rheumatism" as infection with *Coccidioides immitis*. On infection 60 per cent of people remain asymptomatic, while 40 per cent develop symptoms resembling a severe cold or mild pneumonia within one to three weeks following exposure. In 4 to 25 per cent the primary infection is complicated by erythema nodosum and polyarthritis. Lasting immunity follows this hypersensitivity reaction.

Disseminated coccidioidomycosis develops in approximately 0.05 to 0.2 per cent

*Veterans Administration Hospital, Seattle, Washington.

of all cases of primary infection. The mortality for this form is 50 per cent. All organs can be affected, the central nervous system being involved in one-fourth to one-half of the patients, overwhelmingly in the form of meningitis though a few granulomatous encephalitides have also been reported.[4] When the central nervous system is involved the disease is universally fatal. However, one case of a 10 year survival following shunting operations has been reported.[5]

The following laboratory procedures are of value in establishing the diagnosis: isolation of the fungus from the spinal fluid directly or after culture on Sabouraud's medium or by animal inoculation; complement fixation and precipitin tests on blood or spinal fluid, particularly if the titer is rising during the illness;[6] a coccidioidin skin test in which failure to react to a 1:100 dilution skin test indicates strongly against an active process being coccidioidomycosis. A change from negative to positive during the disease is diagnostic.

The sedimentation rate closely parallels the activity of the *Coccidioides* infection. The peripheral blood often shows eosinophilia.[7,8]

DR. W. H. OLDENDORF:* The onset of this man's illness, with fever and signs of pulmonary infection, followed in several weeks by headache and confusion, suggests an infection with manifestations of diffuse neurologic involvement. The cerebrospinal fluid cellular response between October 1943 and June 1944 is further evidence that this was an infectious process involving the central nervous system. The fluctuant clinical course between 1943 and 1948 is not suggestive of a neoplastic process.

The prolonged course, with low-grade fever and a mild leukocytic response, suggests an infectious agent which evoked little immune response. The wide fluctuations of spinal fluid protein with relatively few white cells between 1943 and 1948 are suggestive of varying degrees of loculation of the lumbar subarachnoid space with little circulation of spinal fluid. This is consistent with a granulomatous meningeal reaction.

From the foregoing it would seem that this man was suffering from some relatively nonantigenic infection, which produced a granulomatous reaction in the meninges.

The only detailed neurologic examination was that of November 28, 1947, approximately five months before death. At this time the localizing value of the neurologic examination was somewhat obscured by generalized debility. However, the asymmetric lateral gaze nystagmus, corticospinal signs, and ataxia would suggest the posterior fossa as a site of pathology. The generalized weakness and corticospinal involvement probably invalidated ataxia as a localizing sign.

The laboratory workup it not diagnostic of the etiologic organism. The 7 to 12 per sent eosinophilia noted throughout his illness would suggest a parasitic or mycotic etiology.

The terminal course was that of a diffuse parenchymal cortical involvement with either a bulbar or pseudobulbar palsy.

CLINICAL DIAGNOSIS:

Coccidioidomycosis meningitis.

ANATOMIC DIAGNOSES:

Coccidioidomycosis meningitis.

Coccidioidomycotic granuloma in hilar lymph nodes.

Atrophy of skeletal muscle; pulmonary atelectasis; acute passive congestion of spleen; decubitus ulcers.

PATHOLOGIC DISCUSSION

DR. KNOX FINLEY: The pathologic and neuropathologic findings are consistent with the patient's chronic course and explain some of the unusual features in this patient's prolonged clinical course and atypical laboratory findings. At first, the pathologists were unable to find any *Coccidioides immitis* fungi in the lung. It was only after going back over the material that they

*Veterans Administration Center, Los Angeles, California.

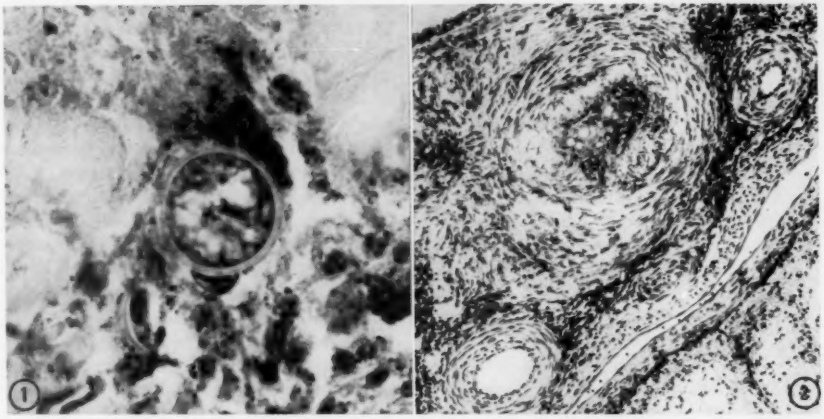

FIG. 1. Section from peribronchial lymph node. The sharply outlined spherical object in the center is a coccidioidomycosis spherule with a clearly defined thick refractile capsule. The cytoplasm is not well defined in this particular spherule, but is one of the stages through which these mother spherules pass before the endospores become well defined. This particular spherule was the only one that was found in the lung tissue and then only after repeated and careful searching. Hematoxylin and eosin stain, high power.
FIG. 2. Meninges at the basis pontis. The thickened pia arachnoid is due to proliferation of fibroblasts, extensive infiltration with mononuclear cells, primarily lymphocytes, and some plasma cells. The thickening of the blood vessel walls is probably due to edema. A large giant cell is shown in the center of which may be seen many endospores. These endospores have at this point ruptured from the mother spherule and their varying sizes indicate varying degrees of maturation. Nissl stain, high power.

came across a single spherule, as illustrated in figure 1. Likewise, we searched long before finding the coccidioidomycosis elements within the subarachnoid space. These were few and in marked contrast to the great abundance of coccidioides found in six cases of coccidioidomycosis meningitis which were previously studied in this neuropathology laboratory. These latter patients had all been ill for a period of only a few months to just under a year. In patients ill less than a year, one has no difficulty in demonstrating the fungus in the subarachnoid space with all its developmental phases, including spherules with endospores and the individual endospores in their various phases of maturation after they have ruptured from the mother spherule.

Autopsy showed no gross changes in the parenchyma of the lungs except for a small area of atelectasis in each lower lobe. Two hilar lymph nodes contained a few whitish, moderately firm areas. Microscopic examination revealed one granulomatous lesion of microscopic size composed of numerous large mononuclear cells and fibroblasts, with connective tissue at the periphery, the latter being partly hyalinized. This lesion was peribronchial to one of the large bronchi. One large mononuclear cell revealed a large round cytoplasmic vacuole with a distinct highly refractile capsule surrounding a faintly pink staining inner area (figure 1). This lesion might be interpreted as a spherule although no endospores were visualized. Heart, spleen, pancreas, adrenals, kidneys, rib, bone marrow, and skeletal muscle were normal except for some nonspecific changes within the liver.

Brain. A thick, yellowish-white exudate was present over the base of the brain, including the interpeduncular and basilar cysterns. The convolutions over the convexities were somewhat flattened and the sulci narrowed. Frontal sections through the hemispheres, brainstem, and cerebellum showed

no gross changes on the cut surfaces. The ependymal lining of both lateral, third, and fourth ventricles had a ground-glass appearance. In the fourth ventricle there were small, peduncular projections measuring 0.5 to 1.0 mm. in diameter. The choroid plexuses in each lateral ventricle were firmly adherent to the ependymal lining.

Microscopic slides showed widespread changes in the pia-arachnoid about the brainstem and interpeduncular fossal and to a lesser extent about the circle of Willis, hippocampus gyrus, and medial base of the temporal lobes. These pia-arachnoid changes consisted of varying numbers of small round cells and plasma cells. The round cell reaction sometimes occurred in concentrated groups, but in other areas it was rather widely dispersed among many cells containing large, vesicular, irregular, spherical, and lima bean-shaped nuclei. There was a varying degree of widespread connective tissue and fibroblastic proliferation, and on a few occasions isolated granulomatous lesions were found, in a very few of which characteristic multi-nucleated giant cells occurred. In occasional instances these giant cells contained spherical bodies of various sizes. The larger of these had double refractile walls, often with an ill-defined cytoplasmic content. In a few, however, definite endospores were seen. There were extra spherule endospores showing various sizes and degrees of maturation (figure 2). Some of the subarachnoid cellular response extended into the superficial portion of the adjacent parenchyma of the perivascular space of the blood vessels. This was particularly true at the base of the brainstem. No significant proliferative response or cellular infiltration was found in the subarachnoid space over the convexities or in the sulci of the cerebral hemispheres. The ependyma of the lateral and third ventricles showed scattered focal subependymal proliferative lesions, with adjacent perivascular round cell infiltration which may have extended into the underlying parenchyma for a distance of 1 to 3 mm. The most extensive ependymal change was found in the fourth ventricle. Here the ependyma was almost entirely replaced by a thick band of proliferative connective tissue and glial response with widespread round cell infiltration. Every so often there was a mound of proliferative cellular response and round cell reaction projecting into the ventricular space 1 to 3 mm.

All the discussants made the correct diagnosis: coccidioidomycosis. In retrospect, as one goes back over the initial details of this patient's illness in August 1943, the patient's early complaints are quite consistent with a primary coccidioidomycosis infection. He had an initial history of an acute febrile illness associated with pleuritic pain in the chest. The roentgenographic findings of a mild acute pulmonary condition and an eosinophilia are likewise compatible. This initial illness subsided, followed by a recurrence associated with chills and fever 11 days later. He improved temporarily, but again relapsed a few days later with more widespread symptoms including severe headache. This, with the confirmatory signs of stiff neck and the abnormalities of spinal fluid, certainly was the signal of the onset of meningeal involvement. Fortunately, as has been pointed out, involvement of the meninges in the process of dissemination only occurs once in 500 to 1,000 cases of mycotic infection. Certainly had this patient been admitted to a hospital in the endemic coccidioidomycosis region of the San Joaquin Valley, the correct diagnosis known as "San Joaquin fever" or "valley fever" would have been made. However, having been admitted to a hospital in a community outside the known endemic area in the San Francisco Bay area, it is understandable how the diagnosis of influenza or nonspecific pneumonia was considered. However, one should have considered coccidioidomycosis meningitis as a differential possibility on the patient's third admission to the same hospital (October 1943) with the development of stiff neck and abnormal spinal fluid findings. They were close to the diagnosis in suspecting tuberculous menin-

gitis. The coccidioidin skin test was probably just out of the experimental laboratory stage at this time and not too well known by clinicians; otherwise this test would have been carried out at the same time as the tests for typhoid, paratyphoid, brucellosis, tularemia, and tuberculosis. A spinal fluid with low sugar and increased protein and cells should always bring coccidioidomycosis meningitis into the differential diagnostic consideration when tuberculous meningitis has been ruled out. This is particularly important in or near a coccidioidomycosis endemic area.

The clinical course over the next five years was remarkable for the chronic periods of exacerbation and remission which occurred. We are again reminded of the importance of considering neurologic etiologies with psychiatric syndromes when we recall that this patient spent 17 months in a psychiatric hospital. The physicians here were certainly aware of the probable neurologic etiology in their diagnosis of psychosis with encephalitis. The second remarkable feature of the clinical course was the variety of hospitals in which the patient was further studied and observed following his initial readmission to a private hospital in San Mateo. Following this the patient was studied and observed in two medical school centers, a Veterans Administration psychiatric hospital, a Navy hospital, and finally the Oakland Veterans Administration Hospital. In this latter hospital the patient had been under observation for a period of several months before the correct diagnosis was seriously entertained and finally made. This was only after an outside physician, Dr. Charles Edward Smith who has contributed so much to our knowledge of the coccidioidomycosis, suggested carrying out some immunologic coccidioidin studies.

I had seen this case on several occasions before the clinical diagnosis was made. I erred in the diagnosis for two reasons: First, in the numerous cases of coccidioidomycosis meningitis which I had seen, all had died within a year from the onset of the disseminated stage of their illness. I was unaware and did not take the occasion to carefully review the literature that occasionally these cases of coccidioidal meningitis can live for more than a year and in one instance for a period of ten years, as referred to in Dr. Leffman's discussion. Secondly, I was influenced too strongly by the relatively high spinal fluid sugars over the past year, even though aware that he had had a few low spinal fluid sugars in the initial course of his illness. This is the first case of coccidioidal meningitis which I have seen in which the spinal fluid sugars had been above 40 mg. per cent.

This case report and table 1 originally appeared in an article by Drs. Edgar Rosen and Joseph Belber entitled "Coccidioidal Meningitis of Long Duration" in Annals of Internal Medicine 34: 796-809, 1951. They are reproduced here by kind permission of the authors and the editors of the Annals.

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CASE REPORT

Chlorpromazine in Thalamic Pain Syndrome

Lester H. Margolis, M.D. and Alfred J. Gianascol, M.D.

IN ITS FULLY DEVELOPED FORM the thalamic pain syndrome constitutes one of the most distressing disorders encountered in medical practice. No satisfactory treatment for it exists, and in refractory cases the aim of therapy is to provide as much relief with as little narcotics as possible, while hoping for a spontaneous remission. In those cases which do not subside spontaneously, analgesic drugs may fail and surgical procedures such as lobotomy offer the only hope for relief.

Chlorpromazine has been little used in this syndrome. In the four cases reported,[1,2] no essential improvement resulted with doses ranging from 50 to 150 mg. administered daily for three to eight days. The following report describes a case in which a gratifying degree of relief was obtained using doses of 200 to 400 mg. This improvement has been sustained for almost a year and a half. Attempts to reduce the dosage or discontinue chlorpromazine have resulted in recurrence of the pain.

CASE REPORT

On September 16, 1953 a 41 year old housewife suddenly developed right hemiplegia with aphasia, homonymous hemianopsia, and hemianesthesia. These functions gradually returned, but her recovery was marred by the development of distressing, burning pain throughout the involved side. This began two weeks after her ictus, persisted unabated during the next nine months, and led to four suicide attempts. She was seen at the Langley Porter Clinic on April 10, 1954 but would not consent to hospitalization until three months later, after having been committed to a mental institution following her fourth suicidal attempt.

Pertinent features in the past history included the divorce of the patient's parents when she was three months of age, two subsequent marriages by her mother, and a home atmosphere characterized by disorganization and strife. From an early age the patient manifested shyness and emotional instability, and at age 29 alcoholism became a problem. At the age of 39, associated with a heavy alcohol intake, the patient was hospitalized for nine days because of a psychotic episode with paranoid features. Although the alcoholism continued, no further complications ensued until the onset of her present difficulties.

Findings on admission to the Langley Porter Clinic on July 16, 1954 were essentially the same as those noted on the patient's first visit three months previously. Although she affected a cheerful facade and presented her complaints in a quiet, controlled manner, her preoccupation with pain was readily apparent. The nutritional status was good and, except for the neurologic findings, the general physical examination was unremarkable. There was slight expressive dysphasia accompanied by mild impairment of intellectual function. Aside from slight right lower facial weakness, no cranial nerve defect was noted. Motor weakness and

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spasticity were present on the right, more pronounced in the upper than in the lower extremity. Deep muscle reflexes were hyperactive on the right. Abdominal skin reflexes were absent and the plantar response equivocal on this side.

Sensory examination revealed findings characteristic of a moderately severe thalamic syndrome. There was elevation of the threshold of all forms of sensation on the right half of the body without true anesthesia. Repetitive stimulation of the skin on the right produced an increase in the burning, disagreeable pain already present. This was likewise exacerbated by active and passive movement of the right extremities and to a lesser extent by respiratory movements. Pronounced hyperpathia, however, was not present. There was no over-reaction to extremes of thermal stimulation, no radiation or lingering aftersensation of pinprick, and, although scraping or tickling produced more discomfort than on the opposite half of the body, no intense withdrawal reaction occurred.

Laboratory findings. A complete blood count, urinalysis, electrocardiogram, and roentgenograms of the skull, spine, and chest revealed no significant abnormalities. Serologic tests for syphilis were negative. An electroencephalogram showed a reduced amplitude on the left, but was interpreted as being within the limits of normal. Psychologic testing, including Rorschach and the Minnesota Multiphasic Personality Inventory, indicated evidence of depression and anxiety, but no suggestion of hysterical or hypochondriacal mechanisms was found.

Course. During the first 18 days of hospitalization the patient remained unaffected by a course of Benadryl, utilizing 600 mg. daily for seven days, or by placebo tablets and injections. Very little relief was obtained with aspirin compound with 65 mg. codeine given as often as every four hours. Except for short periods after receiving 50 to 75 mg. of Demerol orally or parenterally or amobarbital sodium intravenously, she was engrossed with the pain. Her manner was quiet and pleasant and she made no attempt to dramatize her suffering. When pain became unbearable she withdrew to her room, and on such occasions would be found crying softly to herself. She often pleaded for relief, but in a quiet way, and her conversations constantly reverted back to her pain. She could not participate in the usual ward activities or in physiotherapy since she found it necessary at all times to guard the right extremities from motion. Two weekends spent at home during this period were described as miserable.

On the nineteenth day after admission chlorpromazine therapy was begun and all other medications were discontinued. On successive days she received in divided doses 75, 150, and 200 mg. intramuscularly, followed by 250 mg. orally for the next 11 days. By the fourth day the patient reported that the pain was bearable, and after the sixth day she was able to engage in physiotherapy and other activities previously denied her by pain. Two weekends spent at home during this time were described as pleasant and relaxed and the patient expressed a desire to go home to stay.

At this point placebo capsules identical in appearance were substituted for chlorpromazine for a period of five days, two of which were spent at home. During this time, the patient's low grade pain returned to its former unbearable intensity and she renewed her pleas for a lobotomy.

Chlorpromazine was resumed, again a prompt favorable response took place, and 26 days later on September 20, 1954 the patient was discharged on a maintenance dose of 200 mg. daily. She continued on this dosage for the next four months, during which her improvement was sustained.

Comment. This convincing and gratifying degree of improvement, which had by then been in force for a period of five months, appeared to be related entirely to the effect of chlorpromazine. However, it was felt that this observation should be further tested by reducing the chlorpromazine dosage without the patient's knowledge. This was accomplished by substituting 25 mg. capsules which were otherwise identical to the 50 mg. capsules supplied previously. The patient, who was unaware of this dosage reduction from 200 to 100 mg. daily, experienced a substantial increase in the intensity of pain. This continued for a period of ten days and was relieved when her previous dosage was resumed. Subsequently, by varying the dosage, it was found that the optimal degree of comfort was achieved at a level of 400 mg. daily and that additional relief was not produced by further elevation of dosage. The patient attempted to do without the drug in July 1955, but a prompt exacerbation of her symptoms convinced her of her need for it.

The patient has maintained her improvement for a period of 16 months since discharge from the hospital. Pain is still present to a moderate degree, but it has not interfered with household tasks and no additional analgesics have been required.

DISCUSSION

Although this patient's thalamic syndrome was an incomplete one and her response to it was neurotically conditioned, there can

be little doubt that a severe degree of suffering and incapacitation was present. It would not be unreasonable to conclude that the benefit derived from chlorpromazine was two-fold, in that the drug acted to reduce both the emotional response to pain and the thalamic activity and/or irritation responsible for it. This is in agreement with the experience of others[3,4] in utilizing this drug in patients with painful malignancies, but contrary to our findings in treating patients with other types of intractable pain syndromes in which the associated personality disorder has been held to be of major importance.[5]

It may be postulated that the favorable results in this patient, as contrasted with the lack of success reported in other cases of thalamic syndrome treated with chlorpromazine, may be accounted for by factors peculiar to this case or by the fact that inadequate dosage was employed in the unsuccessfully treated patients. The effect of suggestibility in such a severe disorder would be short-lived. Relapses encountered on two occasions when, with the patient unaware of a change, the drug was discontinued or the dosage reduced argues against any such influence.

SUMMARY AND CONCLUSIONS

A case of thalamic pain syndrome in which gratifying and dramatic relief was obtained with chlorpromazine is described. This patient, who had been incapacitated for nine months and who had made four suicidal attempts because of pain, has been maintained in a comfortable state for almost a year and a half on a daily dose of 200 to 400 mg. of chlorpromazine. Two attempts to reduce or withdraw the drug without the patient's knowledge by substituting a less potent or a placebo capsule resulted in recurrence of the intense symptoms. Further investigation of the efficacy of chlorpromazine in the thalamic pain syndrome and in other states characterized by hyperpathia appears to be warranted.

The chlorpromazine used in this study was supplied by Smith, Kline and French Laboratories under the trade name of Thorazine.

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CORRECTION

In the February 1956 issue of Neurology, page 154, legends to figure 3 and figure 5 were transposed erroneously and should be reversed.

CASE REPORT

Neurofibromatosis with Symptoms Secondary to Pheochromocytoma

Bergen Morrison, M.D., I. H. Schuleman, M.D. and J. Stuart Boren, M.D.

ON AN ACTIVE NEUROLOGY SERVICE, patients are often seen complaining of frequent headaches and/or convulsions. We recently had the opportunity to observe a man with a relatively rare combination of disease processes accounting for his headaches and convulsions. Because of the unusual clinical picture and the excellent response to therapy, it was considered worthy of report.

Neurofibromatosis of the nervous system is an heredofamilial disorder of a blastomatous nature.[1] The classic picture is one of skin lesions and multiple neurofibromas on the peripheral nerves. There are also cases with tumors of the nervous system, which include meningiomas as well as neurofibromas.[2] In addition, many diverse anomalies have been recorded in connection with the disease.

The present case report is that of a patient with neurofibromatosis and pheochromocytoma. MacKeith[3] found this association in nine out of 165 cases of pheochromocytoma he reviewed. A tenth case in which neurofibromatosis was associated with pheochromocytoma was reported by Davis.[4] In a review of 15 cases of pheochromocytoma, Minno[5] reported one with associated neurofibromatosis.

CASE REPORT

A 32 year old white truck driver was admitted on November 19, 1954 as a transfer from another hospital. His present illness began on November 8, 1954 with a sudden headache followed by vomiting. Headaches recurred every four to eight hours during the following week, lasting one-half to one hour, with pain more severe frontally. On November 15, 1954 he was first hospitalized elsewhere and had a grand mal seizure on admission. Another such seizure occurred two days later during transfer to a second hospital. He was admitted to the Veterans Administration Hospital, Houston, Texas, two days after that.

Pertinent history obtained from the patient included the fact that since childhood he had had brown spots distributed over his body associated with small nodules. This condition was first diagnosed as neurofibromatosis while he was in military service during World War II. In 1945 a fibroma was removed from his mediastinum. His mother has similar lesions, and his two daughters have the skin discoloration only. The patient was told that he had hypertension as early as 1951. For about one year he had suffered with occasional brief attacks of basilar headaches, "nervousness," and weakness associated with nausea.

Admission examination showed an individual who seemed sleepy and yawned frequently. Blood pressure was 150/100, pulse 120, respiration 32, and temperature 97.6° F. Positive findings included numerous cafe-au-lait lesions and multiple subcutaneous nodules distributed over

From the Veterans Administration Hospital, Houston, Texas, and the departments of psychiatry, neurology, and urology, Baylor University College of Medicine, Houston.

the body. A scar of the previous thoracotomy was present. The right patellar reflex was slightly hyperactive, and the right Babinski sign was equivocal. Routine complete blood count, urinalysis, and serology were considered to be essentially normal. A lumbar puncture done two weeks after onset of this illness showed pink fluid which was under normal pressure, with xanthochromic supernatant fluid and approximately 120,000 red blood cells per cu. mm in each of the three tubes of spinal fluid examined. The electroencephalogram done on admission was interpreted as compatible with subarachnoid hemorrhage; a tracing done about two months later was considered to be within normal limits.

During the next five weeks the patient was nauseated almost daily. A carotid angiogram was scheduled on one occasion but was cancelled when blood pressure of 220/100 was recorded. A review of his chart showed similar elevations of systolic and diastolic blood pressures to the levels of over 200 and 100, respectively. The possibility of pheochromocytoma was thus considered. Left carotid angiogram was performed later and was normal (the patient developed sensitivity to the dye before the angiogram could be done on the right). Since an elevated blood pressure could not be found when Benodaine was available, 0.05 mg. of histamine base was given intravenously, with a prompt rise of blood pressure to 245/130, associated with basilar headache, nausea, trembling, and paleness of the extremities. An intravenous injection of 18 mg. of Benodaine dropped the blood pressure to normal in two minutes. The patient felt sure that histamine had reproduced his headaches. These results indicated that a diagnosis of pheochromocytoma was justified, and the urology service accepted the patient for further study and treatment. On January 26, 1955 the patient had a spontaneous paroxysm, with his blood pressure at 250/130. In addition, there was a reproduction of his symptoms characteristic of his prehospital attacks. The blood pressure returned to normal and the symptoms were relieved with intravenous Regitane, normal blood pressure levels being reached within two minutes. On January 19, 1955 an intravenous pyelogram was obtained which showed no evidence of calculi in the urinary tract. There was prompt excretion in good concentration of the injected Urokon. A downward displacement of the right kidney was noted, with a lateral deviation of its upper pole causing a kink at the ureteropelvic junction. On January 21, 1955 a retrograde pyelogram, presacral pneumoretroperitoneogram, and translumbar aortogram were done under mild sedation and local anesthesia. The films taken were interpreted as excluding a mass on the left but were compatible with a mass on the right. An area of increased vascularity was also noted above the upper pole of the right kidney. On January 28, 1955 surgery was performed and the tumor removed through a right flank incision with removal of the eleventh rib. The tumor lay at the upper pole of the right kidney and was a reddish-brown, egg-shaped mass weighing 35 gm. The cut surface revealed it to be hemorrhagic. The pathologic picture was that of pheochromocytoma. The postoperative course of this patient was rather uneventful. On the third postoperative day the systolic level fell to 100 but quickly stabilized itself with the use of cortisone and DOCA. These medications were gradually reduced over a three day period and no drugs were required after that time. Postoperative follow-up six weeks later disclosed that the patient felt in perfect health and had no further paroxysms. He returned to work one month postoperatively.

On admission to the hospital it was thought that this man had a vascular anomaly as the basis of his illness. The presence of pheochromocytoma was not suspected until he was found to have periods of hypertension. The histamine test produced immediate increased blood pressure which fell to normal range after the injection of an adrenolytic agent.

SUMMARY

1. A case of neurofibromatosis with associated pheochromocytoma producing subarachnoid hemorrhage, episodes of headache, and seizures is reported.

2. He has had no further periods of hypertension or other symptoms since operation.

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APRIL, 1955

AAN St. Louis Meeting Promises New High in Program Interest The 1956 annual meeting of the American Academy of Neurology, which will be held at the Jefferson Hotel, St. Louis (April 23-28), promises exciting innovations and the most comprehensive, national scientific program in neurology ever held. Activities will begin on Monday, April 23, with special review courses in graduate neurologic education under the direction of A. B. Baker. All of these courses will carry a full complement of registrants, including a new course in neurochemistry and a special "grass roots" course for general practitioners under Benjamin Boshes. On the same day (April 23), a distinguished group of clinical neurologic teachers, medical school deans, and medical educators will convene in the country's first national conference on training in clinical neurology; the conference is being sponsored by the Neurology Training Grants Committee of the National Institute of Neurological Diseases and Blindness (see March 1955 Newsletter)....Under the creatively guiding hand of Program Chairman James L. O'Leary, the meeting's annual scientific sessions (Thursday, April 26, through Saturday, April 28), are heavily scheduled with carefully selected papers, and present a rounded program of interest to both practicing and academic neurologists and to experimental scientists. As a special program highlight, a symposium will be held on Thursday evening (April 26), presenting new knowledge and new leads for future investigations on the pyramidal tract (A. M. Lassek, Clinton N. Woolsey, Benjamin Boshes, and A. E. Walker)....Among distinguished foreign visitors at the St. Louis meeting will be Sir Charles Symonds, honorary consultant to the National Hospital, Queen Square, London, who will present a paper on Saturday (April 28) entitled "Otitic Hydrocephalus," and Prof. Dr. G. Schaltenbrand, director of the University Neurological Clinic, Wurzburg, Germany.

Exhibits and Motion Pictures Benjamin Boshes, chairman of the exhibits committee, has prepared an interesting array of exhibits and motion pictures from clinical and laboratory scientists, from voluntary health organizations, and from publishers and technical companies. There will be 17 scientific exhibits in clinical and basic neurology. The former range from the diagnostic and therapeutic aspects of cerebral palsy and muscular dystrophy to newer treatments in parkinsonism

(medical and surgical, including chemopallidectomy); from seizure states in pregnancy and the scalenus anticus syndrome to the management of myasthenia gravis, especially in the pediatric aspects of the disease. Exhibits on basic studies range from temporal lobe suppressor seizures in primates and a study of the temporal horn to quantitative histochemical studies of the nervous system; from newer procedures in electrodiagnostics to those of electrical stimulation and recording from various parts of the brain; from correlations between behavior and brain constituents, particularly enzymes and neurohormones to nervous system architectonics, as defined by recent work in electron miscroscopy. An exhibit of an unusual glioblastic tumor will be presented by Prof. Ihsan Sukru Aksel of Istanbul....Four motion pictures are concerned with the parkinsonlike syndrome in reserpinized monkeys and chimpanzees (Windle and co-workers), a new neurologic sign (Weinberg), a study of lesions in the posterior parietal lobe in trained monkeys (Glass and Cole), and the diagnosis and management of myasthenia gravis (Osserman). There will be program exhibits from the National Multiple Sclerosis Society and the National Society for Crippled Children and Adults. Among the publishers and technical exhibitors are: McGraw-Hill Book Co., Inc., C. V. Mosby Company, Paul B. Hoeber, Inc., Robert Brunner, Inc., E. R. Squibb and Sons, Abbott Laboratories, Sandoz Pharmaceuticals, Wyeth Laboratories, Smith, Kline and French Laboratories, Ciba Pharmaceutical Products, Inc., Grass Instrument Co., and Aloe Scientific Co.

Active Social Calendar Following the spirited tempo of AAN meetings in the past, a lively program of social activities has been planned for the St. Louis meeting. For those who wish to socialize before the scientific sessions begin, arrangements have been made for the traditional Early Bird Party, to be held late Wednesday afternoon in the Jefferson Hotel, followed by a buffet supper (attendance optional) to herald the opening of the Children's Art Bazaar at the Famous-Barr Department Store, the proceeds of which will be given to the Preschool Visually Handicapped Foundation. Local professional artists will be at the Bazaar to sketch the profiles of AAN members for presentation to their wives, students, or friends. The annual AAN cocktail party and banquet will be held Friday evening (April 27) at the Jefferson....The Woman's Auxiliary has prepared an active program, and for free time carefully prepared shopping guides will be available; also, a tour of the Missouri Botanical Gardens has been booked for Friday (April 27).

* * * * * *

Institute of Neurology Created at Washington University Portending the rise of public interest in neurology was the recent gift of a million dollars to endow the Beaumont-May Institute of Neurology at the Washington University School of Medicine in St. Louis. Half of the donation came from the Louis D. Beaumont Foundation of Cleveland, Ohio;

the remainder was contributed by Morton J. May, chairman of the board of May Department Stores Co., and by Mrs. Charles M. Rice in behalf of her family and in memory of her late husband who was an attorney and civic leader. According to Dr. Oliver Lowry, dean of the medical school, the gifts will enable the institution to start a long-range program for research on a group of brain disorders which are becoming increasingly important. "One of the major challenges in the field," he points out, "is the prevention of structural and chemical changes in the brain which may occur at any age and eventually occur in everyone." It is expected that the grant will provide new permanent positions for key investigators and that these funds will be expanded through short-term research grants from national organizations.

House Raises NINDB Budget Two Million Dollars

The House Committee on Appropriations has increased the fiscal year 1957 appropriation of the National Institute of Neurological Diseases and Blindness $2 million over the executive budget request. This action of the House brings the Institute's total budget allowance to $14,196,000, and represents an increase of $4,335,000 over the fiscal year 1956 appropriation. The $2 million increase recommended in the House bill provides for an increase of $1,150,000 for research grants, $200,000 for research fellowships, and $610,000 for training grants. These figures are not necessarily the final NINDB appropriation figures for the fiscal year 1957, since the House bill must be acted upon by the Senate Appropriations Committee.

Research Information Groups Meet in Princeton

On March 7-8, the Subcommittee on Research Information of the National Committee for Research in Neurological Disorders (See July 1954 Newsletter), Glidden L. Brooks, chairman, met with representatives of several voluntary health organizations and foundations for the purpose of exchanging information on their respective programs and on the nature of their grants programs for research on neurologic disorders. Following the opening of the meeting by Dr. Brooks, Dr. Stella Leche Deignan, Director of the Bio-Sciences Information Exchange of the Smithsonian Institution, presented a report on the total number and amount of recorded grants categorized under neurologic disorders. Following her presentation, the representatives of each organization presented a summary of their policies, philosophies, and programs which may influence the future of research in the neurologic field. Among those reporting were: Dr. Brooks for United Cerebral Palsy; Mrs. Alice Fitz Gerald, Association for the Aid of Crippled Children; Richard L. Masland, National Association for Retarded Children; Frederick L. Stone, National Multiple Sclerosis Society; A. T. Milhorat, Muscular Dystrophy Associations of America; Pearce Bailey, Myasthenia Gravis Foundation; Richard K. Anderson, Rockefeller Foundation; Roderick Heffron, The Commonwealth Fund; and Pearce Bailey and Gordon Seger for the National Institute of Neurological Diseases and Blindness. These

reports were followed by free discussions and the formulation of plans for information exchange in the future, as well as future meetings to include other organizations which could not send representatives to the Princeton meeting because of previous commitments.

Intensive Course in Neuromuscular Diseases of Children The Cook County Graduate School of Medicine announces a two-week intensive course in neuromuscular diseases of children with special emphasis on cerebral palsy, to be given by Dr. Meyer A. Perlstein during the period from June 18 to 29. Designed for neurologists, pediatricians, orthopedists, and psychiatrists, the major emphasis of the course will be placed on the practical clinical aspects of therapeutic and rehabilitation procedures for the cerebral palsied. Included in the courses are several field trips to demonstration clinics and treatment centers....The fee for the course is $225, which includes the cost of meals, travel, and accommodations on the various field trips. Registration is limited. Inquiries and communications should be addressed to John W. Neal, Registrar, Cook County Graduate School of Medicine, 707 South Wood Street, Chicago, Ill.

Here and There The American Academy of Neurological Surgery announces its second annual award to the author of the best paper on clinical or laboratory research pertaining to the nervous system. Eligible for the award are physicians currently in training in neurosurgery or those who have completed their training since June 30, 1954. The recipient of the award will be expected to present the paper at the annual meeting of the American Academy of Neurological Surgery in Phoenix, Arizona, November 7-11, 1956. Travel expenses and an honorarium of $100 will be paid. Communications should be sent to Dr. Edwin B. Boldrey, Chairman of the Award Committee, University of California School of Medicine, San Francisco....The Acta Neurologica et Psychiatric Belgica, published in Brussels, is now in its 56th year. This journal, which has an international character, contains proceedings of Belgium Societies of Neurology and Psychiatry, is written in French but many articles are summarized in English and German....A seminar on new technics of neuroanatomy, including electron microscopy of neural tissues, staining methods for synapses, tissue culture studies of neural tissues, and a study of local blood flow in neural tissue, was held at the National Institute of Neurological Diseases and Blindness (Feb. 28) under the auspices of the National Multiple Sclerosis Society....Recently appointed as honorary-corresponding member of the Academy is Prof. Dr. Jose Pereyra-Kafer, president of the Neurological Society of Buenos Aires....

Percy Bailey

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A new aluminum salt aspirin has been announced by Abbott Laboratories, North Chicago, Illinois, under the name of Dulcet tablets (1¼ gr. aluminum acetylsalicylate sugar tablets). This product is free from acetic taste and odor, and has greater physical stability during ordinary shelf life. Each cherry flavored Dulcet contains 1¼ gr. of aspirin as the alumnium salt, which is as readily absorbed as ordinary aspirin. Bottles of 50 and 100 for the home medicine cabinet have a tamper-proof "U-Press-It" cap to prevent children from opening the bottle by accident.

AYERST'S MYSOLINE SUSPENSION

Mysoline Suspension, a new highly palatable dosage form especially designed for the young or difficult epileptic patient with grand mal and psychomotor attacks, has just been released by Ayerst Laboratories, New York. Mysoline is a safe and effective anticonvulsant with a wide margin of safety. The new suspension from of this drug contains 0.25 gm. of primidone per 5 cc. (1 teaspoonful), and is available in bottles of 8 fluidounces. Also available are Mysoline tablets, 0.25 gm. per tablet (scored), in bottles of 100 and 1,000.

FLEXIN EFFECTIVE IN RELIEF OF SKELETAL MUSCLE SPASM

A new compound known as Flexin (Zoxazolamine, McNeil) and indicated for the relief of muscle spasm in musculoskeletal and neurological disorders is reported to have advantages over previously developed agents because it is orally effective, long-lasting and produces minimal side effects. Unrelated to mephenesin, curariform or "tranquilizing" drugs, the new compound Flexin was synthesized and characterized by the staff of McNeil Laboratories, Inc., Philadelphia. McNeil has made it available to physicians in bottles of 50 scored yellow tablets of 250 mg. each. Flexin is described as a "lissive" agent, that is, one that reduces skeletal muscle spasm without interfering with normal muscle power or activity.

Flexin's action is primarily central, in the spinal cord and subcortical areas of the brain. The drug has been found to be slowly absorbed but rapidly metabolized and excreted. Already some patients have undergone daily therapy for as long as 12 months without untoward effects, further evidence of the unusually wide margin of safety found in pharmacologic studies. Flexin's usefulness is in the treatment and rehabilitation of patients with skeletal muscle spasm and spasticity associated with various rheumatic disorders and conditions affecting the brain and spinal cord, including cerebral palsy in children. Flexin's chief advantages were found to be its oral route of administration, long duration of action and minimal side effects. The "remarkably few" side effects were usually controlled by adjustment of dosage. However, it has been observed that diminished spasticity was often accompanied by increased muscular weakness.

Rx Information

Frenquel

Action: FRENQUEL is a completely new *anti-hallucinatory, anti-confusion* drug. FRENQUEL does not sedate *nor* stimulate. Usually 24 hours or more must elapse before clinical improvement takes place. When FRENQUEL is discontinued, prodromal symptoms may recur in about one week.

Even though relief is not observed in all patients, the many dramatic successes already experienced with FRENQUEL in widespread clinical use warrant general trial where acute schizophrenic hallucinations are present.

FRENQUEL is safe...side effects and drug reactions have not been reported. No ill effects have been observed as measured by repeated blood counts, hemoglobin determinations, liver and kidney function tests. Clinical reports show no adverse effect on pulse rate, blood pressure, respiration.[3,4]

Indications: Acute Schizophrenic Hallucinations

Composition: Frenquel (azacyclonol) Hydrochloride is alpha-(4-piperidyl) benzhydrol hydrochloride

Dosage: 20 mg. t.i.d.

Supplied: Bottles of 100 aqua-blue tablets

Complete detailed FRENQUEL Professional Information will be sent upon request.

1. Proctor, R. C.: Report on Frenquel in acute and chronic psychotic states. Presented before the Bowman Gray Medical Society, Winston-Salem, North Carolina, May 16, 1955. 2. Rinaldi, F.; Rudy, L. H., and Himwich, H. E.: The use of Frenquel in the treatment of disturbed patients and psychoses of long duration, Am. J. Psychiat., in press. 3. Fabing, H. D.: Frenquel, a blocking agent against experimental LSD-25 and mescaline psychosis, Neurology 5:319, 1955. 4. Fabing, H. D.: New blocking agent against the development of LSD-25 psychosis, Science 121:208, 1955.

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In many patients, blocks acute schizophrenic hallucinations

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Used in the treatment of acute schizophrenic hallucinations, FRENQUEL usually erases hostile manifestations, promotes a cooperative state, facilitates psychotherapy and ward adjustment.[2] Adjunctively in electroconvulsive therapy, FRENQUEL may help reduce the required number of treatments.[3]

FRENQUEL is safe, virtually free of toxicity; has shown no tolerance or habituation to date.

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*Bonica, J.J.: and Backup, P.H.: *Northwest Med.*, 54:22, Jan., 1955.